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Assessing Innovations in
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IN IXTAPA, MEXICO

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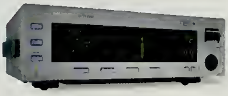

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Editorials, Commentaries, and Reviews To Note

Guidelines for Home Care of Infants, Children, and Adolescents with Chronic Disease—Committee on Children with Disabilities. Pediatrics 1995;96(1):161-164.

A Call to Action: The Institute of Medicine Report on Emergency Medical Services for Children—American Academy of Pediatrics. Pediatrics 1995;96 (1, Suppl):173-210.

Evaluation of Airway Complications in High-Risk Preterm Infants: Application of Flexible Fiberoptic Airway Endoscopy—GJ Downing, HW Kilbride. Pediatrics 1995;95(4):567.

OBJECTIVES: We sought to determine factors that would predict the development of subglottic stenosis (SGS) and tracheomalacia (TM) in preterm infants. The utility of a semiquantitative measurement of airway dimensions was assessed in relation to signs of airway complications. We also sought to determine from a high-risk population of infants those likely to have abnormal findings identified by bronchoscopic examination. METHODS: Prospective airway endoscopy was performed for preterm infants who were intubated for 7 days or more or who demonstrated chronic oxygen needs beyond 28 days after birth and 36 weeks postconceptional age. Subjects were 117 preterm (less than 36 weeks' gestation) infants from two level III intensive care nurseries. Endoscopy was used to classify the type and degree of airway injury. Subglottic stenosis was defined subjectively and compared with an objective measurement using subglottic spatial relations described as a trans-subglottic/vocal cord ratio (TSG/VC). Clinical signs and symptoms and other risk factors were evaluated as significant predictors of SGS and TM, identified by bronchoscopy. RESULTS: Moderate or severe airway abnormalities were identified in 32 patients (27.3%); 13 with SGS, 17 with TM, and 2 with both. All but one infant with TSG/VC less than 0.83 had signs and symptoms of airway dysfunction. Variables more commonly found in patients with SGS included greater number of intubations, use of inappropriately large endotracheal tubes, and longer duration of intubation. Higher averaged mean airway pressure during the first week after birth and lower gestational age were clinical features associated with TM. CONCLUSIONS: Flexible bronchoscopic evaluation of a high-risk population demonstrated a higher incidence of moderate or severe SGS or TM than previously suspected. Subglottic stenosis and TM appear to have different etiologies based on different factors associated with their development. The TSG/VC ratio correlated well with obstructive symptoms and may represent a means to quantitate clinically subglottic narrowing. Infants with chronic lung disease who have persistently elevated partial pressure of carbon dioxide, apnea, or phonation abnormalities are most likely to have airway abnormalities identifiable by bronchoscopy.

Inter-Hospital Transport of Neonatal Patients on Extracorporeal Membrane Oxygenation: Mobile-ECMO—MJ Heulitt, BJ Taylor, SC Faulkner, LL Baker, CW Chipman, JH Harrell, SH VanDevanter. Pediatrics 1995;95(4):562.

OBJECTIVE: To describe the equipment, personnel requirements, training, management techniques, and logistic problems encountered in the design and implementation of a mobile extracorporeal membrane oxygenation (ECMO) program. DESIGN: This is a report of a technique for the transport of patients on ECMO and a description of our retrospective case series. SETTINGS: The study was conducted at a regional referral children's hospital and ECMO unit. PATIENTS: Thirteen neonatal medical patients with acute respiratory failure were transported with mobile-ECMO. RESULTS: Over a 24-month period, we transported 13 neonatal patients with mobile-ECMO. The reason for transport with mobile-ECMO was inability to convert from high-frequency ventilation (4 of 13), patient already on ECMO (1 of 13), and patient deemed too unstable for conventional transport (8 of 13). Eleven of the 13 patients were transported from other ECMO centers. Of the 13, 9 survived. No major complications during transport were reported for any of the patients. Follow-up data were available on all nine survivors of neonatal mobile-ECMO. Eight of these had normal magnetic resonance imaging scans of the brain; the ninth had a small hemorrhage in the left cerebellum. CONCLUSION: Our limited series shows that patients can be safely transported with mobile-ECMO. This program does not replace the early appropriate transfer for ECMO-eligible patients to an ECMO center.

Venovenous Extracorporeal Membrane Oxygenation Affects Renal Function—BJ Roy, JD Cornish, RH Clark. Pediatrics 1995;95(4):573.

OBJECTIVE: We evaluated the effect of venovenous extracorporeal membrane oxygenation (ECMO) on renal function and fluid balance in neonates with severe respiratory failure. DESIGN: We retrospectively reviewed the charts of 30 consecutive patients who met criteria for treatment with ECMO. Twelve were managed without ECMO (comparison group) and 18 were treated with venovenous ECMO (treatment group). SETTING: The study was conducted in a single level III neonatal intensive care unit in a regional children's hospital accepting medical and surgical neonatal transfers. Our hospital does not have an inborn service. PATIENTS: Neonates were included if their gestational age was more than 34 weeks, they weighed more than 2 kg, and their respiratory failure was severe enough to warrant consideration of ECMO as a mode of support. All the neonates in this study were treated with high-frequency ventilation before being considered for ECMO; none were treated with nitric oxide. Criteria used to determine whether a neonate was a candidate for ECMO included: (1) alveolar-arterial oxygen difference greater than 60 kPa (610 torr) for 8 hours; (2) alveolar-arterial oxygen difference greater than 59 kPa (605 torr) and a peak airway pressure greater than 3.7 kPa (38 cm H_2O) for 4 hours; (3) oxygenation index greater than 40 on three of five postductal blood gases obtained at least 30 minutes apart and unstable patient condition; or (4) refractory, severe respiratory failure with sudden decompensation (partial pressure of arterial oxygen 3.4 kPa or lower, 35 torr) despite maximal medical management for 2 hours.

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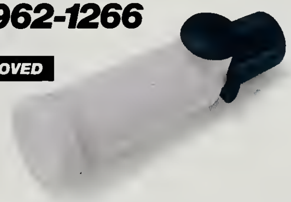

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REFERENCES 1. Data on file HealthScan Products Inc. 2. Wheeler BB, Bollers ND. Initial experience with a novel spacer device (Presented at the 1993 meeting of the American Academy of Allergy and Immunology) * U.S. Patent No. 5,040,527 OA760004-0 © 1994, HealthScan Products Inc

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We did not include patients with congenital diaphragmatic hernia. MAIN RESULTS: There were no differences between the groups in gestational age, birthweight, age at admission, gender, or diagnoses. Over the course of the 108 hours reviewed for each case, neonates treated with ECMO had higher positive fluid balance ($p < 0.001$), lower urine flow rates ($p < 0.01$), and higher blood urea nitrogen ($p < 0.01$) and creatinine ($p < 0.01$) levels than neonates managed without ECMO. There were no differences in mean blood pressure, protein intake, serum albumin, or use of diuretic therapy that might explain the differences between the groups. CONCLUSION: We conclude that venovenous ECMO is associated with transient impairment in renal function and marked fluid retention.

Effects of Early Dexamethasone Therapy on Pulmonary Mechanics and Chronic Lung Disease in Very Low Birthweight Infants: A Randomized, Controlled Trial—M Durand, S Sardesai, C McEvoy. Pediatrics 1995;95:584.

OBJECTIVE: To determine the changes in pulmonary mechanics before and during early dexamethasone therapy, and to evaluate the effect of dexamethasone on the duration of mechanical ventilation in very low birthweight (VLBW) ventilator-dependent infants at risk for chronic lung disease (CLD). METHODS: A prospective randomized trial was conducted. Forty-three patients (birthweight 600 to 1500 g, gestational age 24 to 32 weeks) who failed to be weaned from the respirator at 7 to 14 days of age were enrolled; 23 infants received a 7-day course of dexamethasone (0.5 mg/kg/day intravenously for 3 days, 0.25 mg/kg/day for 3 days, and 0.1 mg/kg/day for 1 day), and 20 patients were in the control group. At similar mean airway pressure (MAP) and fractional inspired oxygen concentration (F_{IO_2}), respiratory system mechanics were measured before and on days 2, 5, and 7 of the study. Airway pressure, flow, and tidal volume (V_T) were recorded and only mechanical breaths were analyzed. Respiratory compliance (C_{rs}) and respiratory resistance (R_{rs}) were calculated by two factor least mean square analysis. RESULTS: Eighty-three percent of infants in the dexamethasone group and 90% in the control group received surfactant in the first 24 hours of life. There was a significant increase in C_{rs} and V_T in the dexamethasone group as compared with the control group ($p < 0.001$). No major changes in R_{rs} were observed. Dexamethasone therapy significantly decreased F_{IO_2} and MAP ($p < 0.001$) and facilitated successful weaning from mechanical ventilation. In addition to a shorter duration of mechanical ventilation ($p < 0.01$), the occurrence of CLD ($F_{IO_2} > 0.21$ at 36 weeks of corrected gestational age, chest radiograph changes) was significantly decreased in the dexamethasone group ($p < 0.01$). Except for a transient increase in blood pressure and serum glucose, there were no significant differences in infection rates, intraventricular hemorrhage, or retinopathy of prematurity. Thirteen patients in the control group received dexamethasone at a later age. CONCLUSIONS: Our findings indicate that: (1) early dexamethasone therapy in VLBW infants markedly improves respiratory compliance and tidal volume, reduces F_{IO_2} and MAP requirements, and facilitates extubation in these infants; (2) early dexamethasone therapy reduces the duration of mechanical ventilation and decreases CLD (at 28 days and 36 weeks) in a population of VLBW infants largely treated with surfactant.

A Computer Algorithm for Differentiating Valid from Distorted Pulse Oximeter Waveforms in Neonates—JA Adams, IM Inman, SA Abreu, IA Zabaleta, MA Sackner. Pediatr Pulmonol 1995;19:307.

Current pulse oximeter technology is fraught with a significant false alarm rate. This is mainly due to motion artifacts at the sensor site which distort the pulse waveform and render the computation of S_{aO_2} invalid. If the pulse waveform could be automatically recognized as either normal or distorted, then only valid S_{aO_2} values would be displayed. We observed that the systolic upstroke time (Sy) of the pulse waveform has a narrow and consistent range in normal appearing pulses. The systolic upstroke time (Sy) is the time from the onset of systole to the peak of the pulse waveform. Comparison of a preset range of Sy was made against Sy obtained by computer analysis of each pulse waveform. Visual examination of 14,090 pulses was carried out to determine the sensitivity and false-positive rate of the algorithm. Sensitivity of computer detection of valid pulses was 92% with a positive predictive value of 92%. When used on line for continuous recording of S_{aO_2} in patients, this simple algorithm has the potential to decrease the false alarm rate of pulse oximeters and improve the accuracy of long-term S_{aO_2} recordings.

The Single Breath Test in Neonates: Does Pressurization of the Pneumotachograph Make a Difference?—AL Coates, ME Fletcher, I Dundas, J Stocks. Pediatr Pulmonol 1995;19:299.

The single-breath test for the measurement of respiratory system resistance and compliance in newborns consists of an end-inspiratory occlusion which is subsequently released, allowing expiration to proceed through a pneumotachograph (PNT). The measured flow is then integrated to give volume. The simplicity of the test is one of the major reasons for its popularity. However, some investigators have cautioned against the use of an occlusion distal to the PNT because pressurization of the PNT may introduce artifacts in the flow measurement. Despite this caution, many commercial systems use a pressurized PNT. This study investigated the errors that would result from pressurization of the PNT by providing a step function of flow to two infant PNTs, a Fleisch #0 and a Hans Rudolph 4500, in the unpressurized and pressurized state. In each case there was an initial rapid rise of the flow signal, followed by some overshoot and oscillations that rapidly died out. The overshoot and oscillations for the Hans Rudolph PNT were greater when pressurized; whereas, pressurization had little effect on the Fleisch PNT. Unpressurized, the two were similar. In either case, the artifact introduced by pressurization of the PNT died out so quickly that it would have little effect on any measurement in an infant.

Dose-Response to Inhaled Nitric Oxide in Acute Hypoxemic Respiratory Failure of Newborn Infants: A Preliminary Report—C Bührer, G Merker, K Falke, H Versmold, M Obladen. Pediatr Pulmonol 1995;19:291.

In acute hypoxemic respiratory failure of term and near-term neonates, extra- and intrapulmonary right-to-left shunting contribute to refractory hypoxemia. Inhaled nitric oxide (NO) decreases pulmonary arterial pressure and improves ventilation-perfusion mismatch in a variety of animal models and selected human patients. We report on 10 consecutive term and near-term newborns with severe acute hypoxemic respiratory failure due to diaphragmatic hernia. meconium aspiration syndrome, group B streptococcus sepsis, pneumonia or acute respiratory distress syndrome, who received increasing doses of inhaled NO (up to 80 ppm) to improve the arterial partial pressure of oxygen (P_{aO_2}). The response to NO and the optimum NO concentration which improved P_{aO_2} varied considerably between patients. Improvement of P_{aO_2} was absent or poor (less than 10 mm Hg) in the 4 newborns with meconium aspiration syndrome and in 1 patient with congenital diaphragmatic hernia, while in the other 5 patients inhaled NO increased the mean (± SE) P_{aO_2} from 41 ± 6 to 57 ± 9 mm Hg ($p < 0.05$). Optimum NO concentrations determined by dose-response measurements performed during the first 8 hr of NO inhalation were 8-16 ppm except for 2 newborns with congenital diaphragmatic hernia who required 32 ppm to effectively increase P_{aO_2}. Four of the 5 patients in whom the P_{aO_2} rose by more than 10 mm Hg received inhaled NO for extended periods of time (5 to 23 days) with no signs of tachyphylaxis. The optimum NO concentration dropped to less than 3 ppm after prolonged mechanical ventilation or when intravenous prostacyclin was given concomitantly. The response to inhaled NO and the optimum NO concentration to improve arterial oxygenation were virtually identical with conventional and high-frequency-oscillatory ventilation (HFO). We conclude that the optimal concentration of NO to improve P_{aO_2} of neonates with acute hypoxemic respiratory failure varies considerably between patients, shows temporal variations, and requires individual and repeated adjustments of the concentration of inhaled NO.

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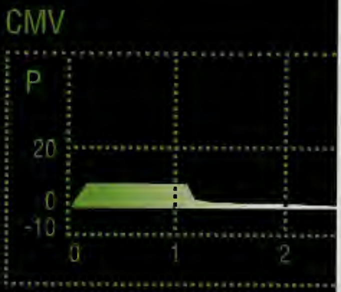

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Functional Residual Capacity (FRC) Measurements by Plethysmography and Helium Dilution in Normal Infants—K McCoy, RG Castile, ED Allen, DA Filbrun, RL Flucke, E Bar-Yishay. Pediatr Pulmonol 1995;19:282.

Comparative measurements of functional residual capacity (FRC) made by plethysmography (FRC_{pleth}) and by helium dilution (FRC_{He}) were obtained on 27 infants and young children without known pulmonary disease (14 males, 13 females; 4 weeks-26 months; mean age 32.2 weeks) while under chloral hydrate sedation. Clinical histories, clinical examinations, and pulmonary functions were normal for all members of the group. FRC_{pleth}, whether measured near end expiration (EE) or near end inspiration (EI), and corrected to mean expiratory levels of at least 3 breathing cycles, was consistently and significantly greater than FRC_{He}. Comparative values for mean (± standard deviation) were FRC_{pleth} EE, 182.0 (± 79.7) mL and FRC_{pleth} EI, 171.8 (± 77.4) mL vs FRC_{He}, 154 (± 72.2) mL, $p < 0.0001$ and $p < 0.005$, respectively. Normalizing values by weight, FRC_{pleth} EE was 23.8 (± 5.3) mL/kg vs FRC_{He}, 20.2 (± 4.7) mL/kg, mean (± standard deviation). The difference between FRC_{pleth} and FRC_{He}, expressed as $FRC_{pleth} - FRC_{He}/FRC_{pleth} \times 100$, was 9% for occlusions at end inspiration and 16% for occlusions at end expiration. The following equations describe our FRC results in relation to length: ln

$$
\begin{gathered}
(FRC_{He}) = 2.74 \times \ln(\text{length}) - 6.53 \\
r^2 = 0.781 \\
\text{slope} = 2.74 \pm 0.29 \text{ SE} \\
Y \text{ intercept} = 6.53 \pm 1.12 \text{ SE} \\
\ln(FRC_{pleth} \text{ EI}) = 2.69 \times \ln(\text{length}) - 6.21 \\
r^2 = 0.752 \\
\text{slope} = 2.69 \pm 0.31 \text{ SE} \\
Y \text{ intercept} = 6.21 \pm 1.29 \text{ SE}
\end{gathered}
$$

The difference between FRC_{pleth} and FRC_{He} was more marked when occlusions were performed at end expiration than at end inspiration. We conclude that normal infants and young children, at least when studied supine and sedated, have a small but significant amount of airway closure.

Does Continuous Positive Airway Pressure (CPAP) during Weaning from Intermittent Mandatory Ventilation in Very Low Birthweight Infants Have Risks or Benefits? A Controlled Trial—JL Tapia, A Bancalari, A González, ME Mercado. Pediatr Pulmonol 1995;19:269.

OBJECTIVE: The purpose of this study was to evaluate three ventilator weaning strategies and to evaluate whether the use of continuous positive airway pressure (CPAP) via a nasopharyngeal or endotracheal tube would increase the likelihood of extubation failure in very low birthweight (VLBW) infants. STUDY DESIGN: We studied prospectively 87 preterm infants (mean ± SD; birthweight: 1078 ± 188 g; gestational age: 28.8 ± 2.2 weeks) who were in the process of being weaned from intermittent mandatory ventilation (IMV). Infants were assigned by systematic sampling to one of the following three treatment groups: (1) direct extubation from IMV (D.EXT) (n = 30); (2) pre-extubation endotracheal CPAP (ET-CPAP) for 12-24 hr (n = 28); or (3) post-extubation nasopharyngeal CPAP (NP-CPAP) for 12-24 hr (n = 29). Failure was defined as the need for resumption of mechanical ventilation within 72 hr of extubation due to frequent or severe apnea and/or respiratory failure ($pH < 7.25$, $P_{aCO_2} > 60$ mm Hg, and/or requirement for oxygen $F_{IO_2} >$ 60%). RESULTS: There were no significant differences in failure rates among the three procedures. Failures were 2/30 (7%) in D.EXT; 4/28 (14%) in ET-CPAP; and 7/29 (24%) in the NP-CPAP. There were also no differences in F_{IO_2}, P_{aO_2}, and respiratory rates before and after discontinuation of IMV among the three groups. P_{aCO_2} values were slightly higher in the NP-CPAP group 12-24 hr after weaning from IMV. CONCLUSION: We were unable to demonstrate a clear difference in extubation outcome by use of CPAP administered via an endotracheal or nasopharyngeal tube when compared to direct extubation from low-rate IMV in VLBW infants.

The Use of Capnography for Recognition of Esophageal Intubation in the Neonatal Intensive Care Unit—WA Roberts, WM Maniscalco, AR Cohen, RS Litman, A Chhibber. Pediatr Pulmonol 1995;19:262.

Failure to recognize esophageal intubation can result in severe hypoxia and permanent neurologic injury. Capnography is a standard monitoring modality in the operating room but has not been utilized fully in other environments. We used capnography at the time of endotracheal intubation in the neonatal intensive care unit (NICU) to determine whether capnography could more quickly and accurately identify endotracheal tube position than other clinical indicators of endotracheal tube position. One hundred intubation episodes were studied in 55 neonates. Capnograms were obtained 15 and 120 sec following tube placement. Intubating personnel were blinded to the capnographic data and determined endotracheal tube location (trachea vs esophagus) by clinical criteria only. The sensitivity and specificity of capnography and clinical examination for identification of tube position were analyzed, and the time required for establishing by clinical confirmation whether the tube was in the trachea or not was compared to that required for capnography. Forty of 100 intubation attempts resulted in esophageal intubation. Capnography correctly identified these errant tube placements in 39 of 40 instances and did so in 1.6 sec (SD ± 2.4). Capnography failed to identify successful endotracheal intubation on only one occasion. Clinical indicators of tube position required 97.1 sec (SD ± 92.6) to identify an esophageal intubation and failed to identify successful endotracheal intubation in 5 of 60 cases. We conclude that capnography is a valuable adjunct to clinical examination to demonstrate whether an endotracheal tube is placed correctly in the trachea of neonates in the NICU.

Electrocardiographic Monitoring during Cardiac Rehabilitation—SJ Keteyian, PA Mellett, FJ Fedel CM McGowan, PD Stein. Chest 1995; 107(5):1242.

STUDY OBJECTIVE: This investigation compares the frequency of cardiac events during ECG-monitored cardiac rehabilitation in patients who meet the American College of Cardiology (ACC) criteria for monitoring, to the frequency of events in patients in the same program who do not meet the ACC criteria. DESIGN AND PATIENTS: Patient charts (n = 289) from a 10-month period were retrospectively reviewed for (1) major and minor cardiovascular events, (2) whether a physician was contacted, and (3) what change, if any, was made in their care plan as a result. RESULTS: There were no sudden deaths, fatal or nonfatal myocardial infarctions, or sustained arrhythmias requiring hospitalizations. The overall rate for minor events (angina, nonsustained arrhythmia, ST segment depression) was 26.6%, with no difference noted between men and women. The rate for a new-onset, asymptomatic event was 3.8%. The rate of minor events was greater in patients who met the ACC criteria vs those who did not ($p < 0.01$), with no detectable difference noted between the two groups regarding the rate of new-onset, asymptomatic events. Four patients (1.4%) experienced a change in their care plan as a result of ECG monitoring. CONCLUSIONS: The occurrence of a minor cardiovascular event is common during phase 2 cardiac rehabilitation, and existing criteria satisfactorily distinguish those patients at high risk for experiencing such an event. However, the rate for new-onset, asymptomatic events is rare for both patients classified at high risk and those classified not to be at high risk. Also, only four patients experienced a change in therapy secondary to an event identified by ECG monitoring. *See the related editorial: **Cardiac Rehabilitation and Health-Care Reform**—CJ Lavie, RV Milani. Chest 1995;107(5):1189-1190.*

Is Tracheal Gas Insufflation an Alternative to Extrapulmonary Gas Exchangers in Severe ARDS?—M Belghith, L Fierobe, F Brunet, M Monchi, JP Mira. Chest 1995;107(5):1416.

Tracheal gas insufflation (TGI) of pure oxygen combined with mechanical ventilation decreases dead space and increases CO_2 clearance. In the present study, TGI was used in six patients with ARDS who met extracorporeal membrane oxygenation criteria and who were severely hypoxemic and hypercapnic despite optimal pressure-controlled ventilation. This open clinical study aimed to investigate the effects of 4 L/ min con-

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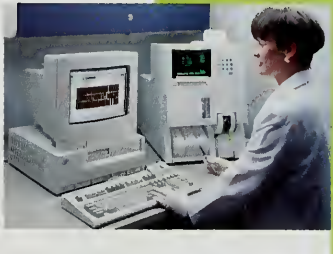

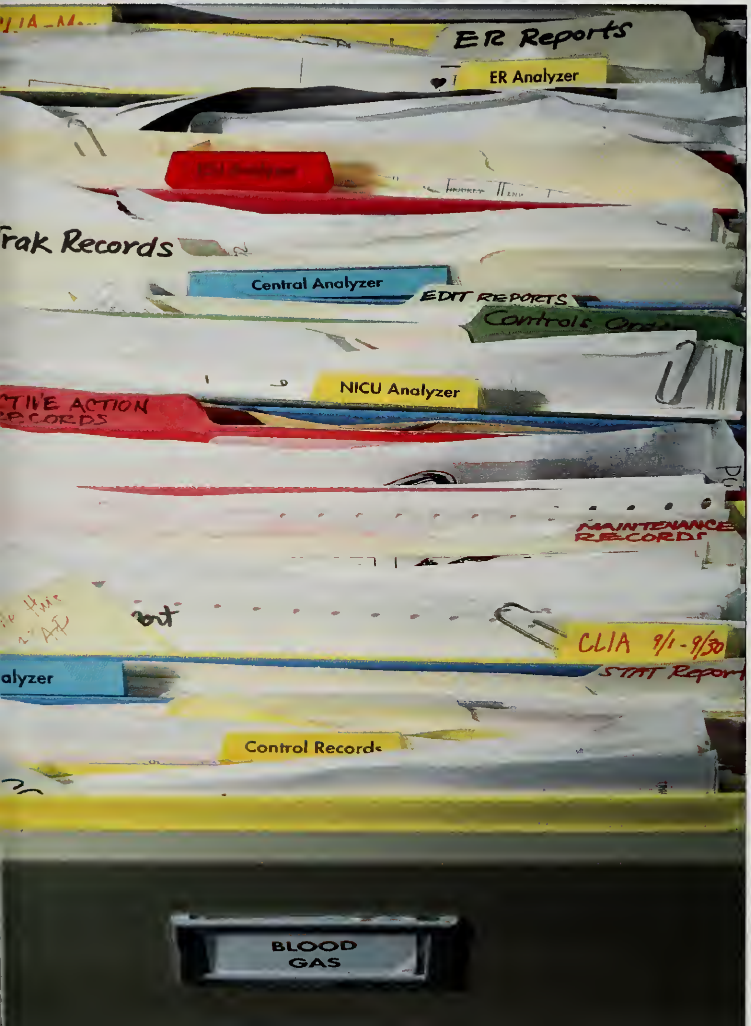

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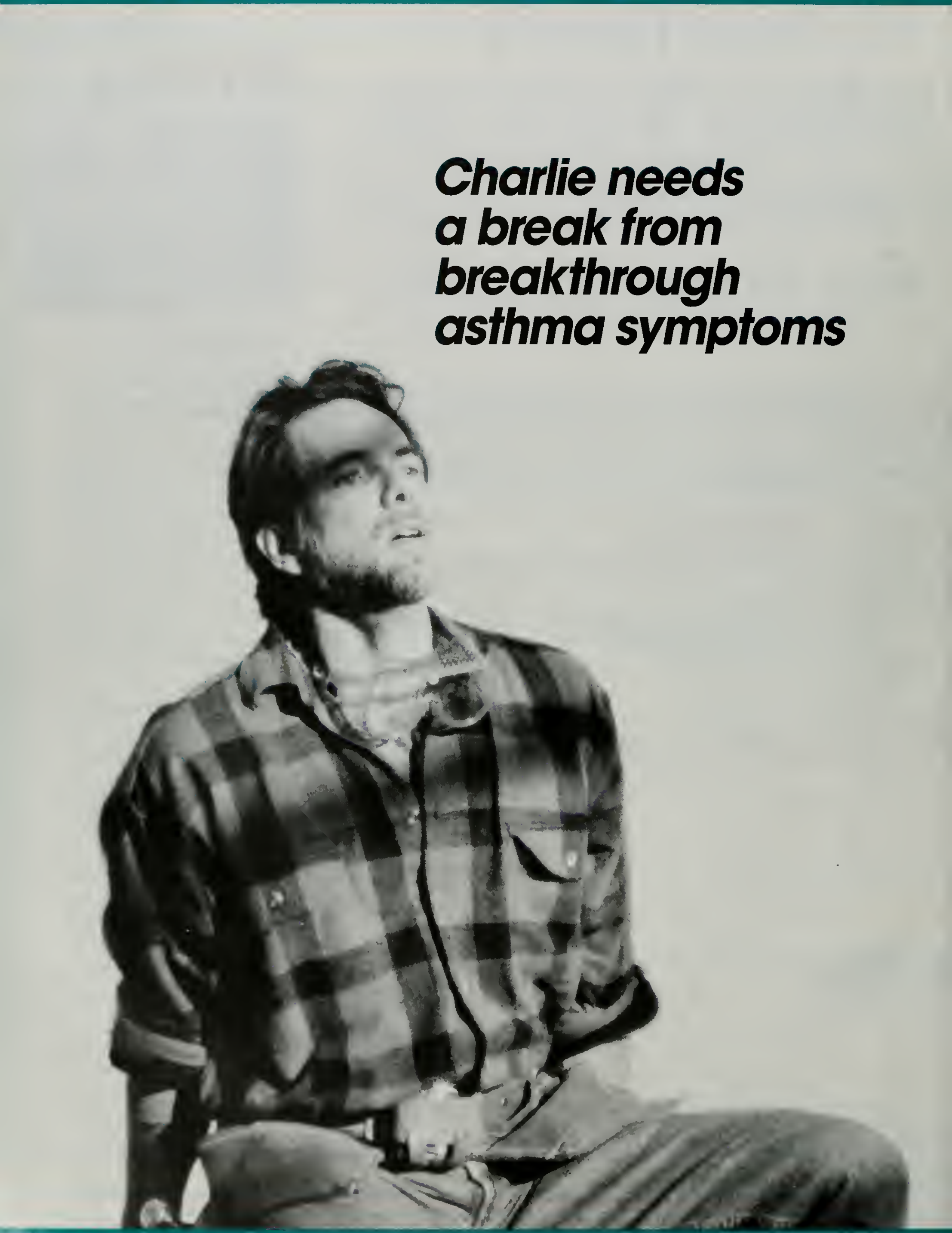
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a break from
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asthma symptoms

Serevent®
(salmeterol xinafoate)

Serevent®
(salmeterol xinafoate)
Inhalation Aerosol

BRIEF SUMMARY

Bronchodilator Aerosol
For Oral Inhalation Only

The following is a brief summary only. Before prescribing, see complete prescribing information in Serevent® Inhalation Aerosol product labeling.

CONTRAINDICATIONS: Serevent® Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of the components.

WARNINGS:
IMPORTANT INFORMATION: SEREVENT® INHALATION AEROSOL SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported, both in the US and worldwide, when Serevent Inhalation Aerosol has been initiated in this situation.

Although it is not possible from these reports to determine whether Serevent Inhalation Aerosol contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of Serevent Inhalation Aerosol in this setting is inappropriate.

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe a short-acting, inhaled beta$_2$-agonist for this purpose as well as warn them that increasing inhaled beta$_2$-agonist use is a signal of deteriorating asthma.

SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when Serevent Inhalation Aerosol is initiated.

(See PRECAUTIONS: Information for Patients section of the full prescribing information and the separate PATIENT'S INSTRUCTIONS FOR USE leaflet.)

1. Do Not Introduce Serevent Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma: Serevent Inhalation Aerosol is intended for the maintenance treatment of asthma (see INDICATIONS and USAGE section of the full prescribing information) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that Serevent Inhalation Aerosol provides greater efficacy than or additional efficacy to short-acting, inhaled beta$_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the US and worldwide, in patients receiving Serevent Inhalation Aerosol. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications, increasing need for inhaled short-acting beta$_2$-agonists, increasing need for systemic corticosteroids, significant increase in symptoms, recent emergency room visits, sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

2. Do Not Use Serevent Inhalation Aerosol to Treat Acute Symptoms: A short-acting, inhaled beta$_2$-agonist, not Serevent Inhalation Aerosol, should be used to relieve acute asthma symptoms. When prescribing Serevent Inhalation Aerosol, the physician must also provide the patient with a short-acting, inhaled beta$_2$-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice daily (morning and evening) use of Serevent Inhalation Aerosol.

When beginning treatment with Serevent Inhalation Aerosol, patients who have been taking short-acting, inhaled beta$_2$-agonists on a regular basis (e.g., q.i.d.) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute asthma symptoms while taking Serevent Inhalation Aerosol (see PRECAUTIONS: Information for Patients).

3. Watch for Increasing Use of Short-Acting, Inhaled Beta$_2$-Agonists, Which Is a Marker of Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's short-acting, inhaled beta$_2$-agonist becomes less effective or the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses four or more inhalations per day of a short-acting, inhaled beta$_2$-agonist for 2 or more consecutive days, or if more than one canister (200 inhalations per canister) of short-acting, inhaled beta$_2$-agonist is used in an 8-week period in conjunction with Serevent Inhalation Aerosol, then the patient should consult the physician for re-evaluation. **Increasing the daily dosage of Serevent Inhalation Aerosol in this situation is not appropriate. Serevent Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose of two inhalations.**

4. Do Not Use Serevent Inhalation Aerosol as a Substitute for Oral or Inhaled Corticosteroids: There are no data demonstrating that Serevent Inhalation Aerosol has a clinical anti-inflammatory effect and could be expected to take the place of, or reduce the dose of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating Serevent Inhalation Aerosol. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

5. Do Not Exceed Recommended Dosage: As with other inhaled beta$_2$-adrenergic drugs, Serevent Inhalation Aerosol should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT interval, which has the potential for producing ventricular arrhythmias.

6. Paradoxical Bronchospasm: As with other inhaled asthma medication, paradoxical bronchospasm (which can be life threatening) has been reported following the use of Serevent Inhalation Aerosol. If it occurs, treatment with Serevent Inhalation Aerosol should be discontinued immediately and alternative therapy instituted.

7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of Serevent Inhalation Aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, and bronchospasm.

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving Serevent Inhalation Aerosol.

PRECAUTIONS:

General: 1. Use With Spacer or Other Devices: The safety and effectiveness of Serevent® Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of Serevent Inhalation Aerosol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects: Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. No effects on glucose have been seen with Serevent Inhalation Aerosol at recommended doses. Administration of beta$_2$-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrhythmias. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of Serevent Inhalation Aerosol at recommended doses.

Information for Patients: See illustrated Patient's Instructions for Use leaflet. **SHAKE WELL BEFORE USING**

It is important that patients understand how to use Serevent Inhalation Aerosol appropriately and how it should be used in relation to other asthma medications they are taking. Patients should be given the following information:

1. Shake well before using.

2. The recommended dosage (two inhalations twice daily, morning and evening) should not be exceeded.

3. Serevent Inhalation Aerosol is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with a short-acting, inhaled beta$_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).

4. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma.

- Decreasing effectiveness of short-acting, inhaled beta$_2$-agonists
- Need for more inhalations than usual of short-acting, inhaled beta$_2$-agonists
- Use of four or more inhalations per day of a short-acting beta$_2$-agonist for 2 or more days consecutively
- Use of more than one canister of a short-acting, inhaled beta$_2$-agonist in an 8-week period (i.e., canister with 200 inhalations)

5. Serevent Inhalation Aerosol should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with Serevent Inhalation Aerosol.

6. Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain, related to the use of additional beta$_2$-agonist.

7. In patients receiving Serevent Inhalation Aerosol, other inhaled medications should be used only as directed by the physician.

8. When using Serevent Inhalation Aerosol to prevent exercise-induced bronchospasm, patients should take the dose at least 30 to 60 minutes before exercise.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical trials (n=184), the mean daily need for additional beta$_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least eight inhalations per day at least on one occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over four inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than eight inhalations per day of short-acting beta$_2$-agonists with Serevent Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving Serevent Inhalation Aerosol, nebulized albuterol (one dose in most) led to improvement in forced expiratory volume in 1 second (FEV$_1$) and no increase in occurrence of cardiovascular adverse events.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of Serevent Inhalation Aerosol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving Serevent Inhalation Aerosol has not been completely evaluated. In one clinical trial, 87 patients receiving Serevent Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving Serevent Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by Serevent Inhalation Aerosol therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m^2]). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/m^2 basis).

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No blastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally (about 160 times the recommended clinical dose on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to the equivalent of about 160 times the recommended clinical dose on a mg/m^2 basis. Dutch rabbit fetuses exposed to salmeterol xinafoate *in utero* exhibited effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10 mg/kg given orally (approximately 1,600 times the recommended clinical dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with Serevent Inhalation Aerosol in pregnant women. Serevent Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Serevent Inhalation Aerosol during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans. In lactating rats dosed with radiolabeled salmeterol, levels of radioactivity were similar in plasma and milk. In rats, concentrations of salmeterol in plasma and milk were similar. The xinafoate moiety is also transferred to milk in rats at concentrations of about half the corresponding level in plasma. However, since there is no experience with use of Serevent Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Serevent Inhalation Aerosol in children younger than 12 years of age have not been established.

Geriatric Use: Of the total number of patients who received Serevent Inhalation Aerosol in all clinical studies, 241 were 65 years and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in four well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in two large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the two latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

No apparent differences in the efficacy and safety of Serevent Inhalation Aerosol were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta$_2$-agonists, however, special caution should be observed when using Serevent Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

ADVERSE REACTIONS: Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, i.e., tachycardia, palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor, nervousness; and paradoxical bronchospasm (see WARNINGS).

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent® Inhalation Aerosol in patients 12 years of age and older with asthma. The following table reports the incidence of adverse events in these two studies.

Adverse Experience Incidence in Two Large 12-Week Clinical Trials*

Adverse Event Type	Percent of Patients		
	Placebo n=187	Serevent 42 mcg b.i.d. n=184	Albuterol 180 mcg q.i.d. n=185
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

* The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug related or nondrug related by the investigator) that occurred at a rate of over 3% in the Serevent Inhalation Aerosol treatment group and were more common in the Serevent Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the Serevent Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.
Ear, Nose, and Throat: Rhinitis, laryngitis.
Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.
Hypersensitivity: Urticaria.
Mouth and Teeth: Dental pain.
Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.
Neurological: Nervousness, malaise/fatigue.
Respiratory: Tracheitis/bronchitis.
Skin: Rash/skin eruption.
Urogenital: Dysmenorrhea.

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

Postmarketing Experience: In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

Postmarketing experience includes rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking.

OVERDOSAGE: Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_c interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

In these cases, therapy with Serevent® Inhalation Aerosol and all beta-adrenergic–stimulant drugs should be stopped, supportive therapy provided, and judicious use of a beta-adrenergic blocking agent should be considered, bearing in mind the possibility that such agents can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

As with all sympathomimetic pressurized aerosol medications, cardiac arrest and even death may be associated with abuse of Serevent Inhalation Aerosol.

Rats and dogs survived the maximum practicable inhalation doses of salmeterol of 2.9 and 0.7 mg/kg, respectively. The maximum nonlethal oral doses in mice and rats were approximately 150 mg/kg and >1,000 mg/kg, respectively.

Dialysis is not appropriate treatment for overdosage of Serevent Inhalation Aerosol.

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References:

1. Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. N Engl J Med. *November 1992;327:1420-1425.* **2.** *D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma.* JAMA. *May 1994;271: 1412-1416.*

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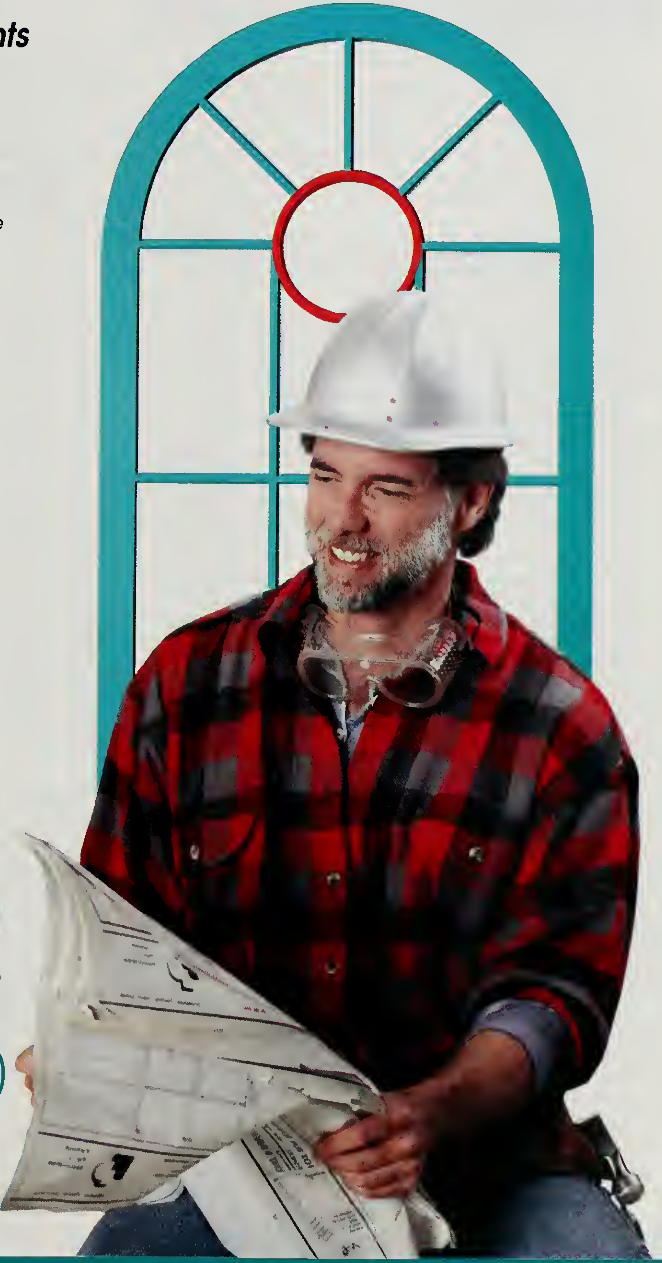

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Reduced Expression of Endothelial Nitric Oxide Synthase in the Lungs of Patients with Pulmonary Hypertension—A Giaid, D Saleh. N Engl J Med 1995;333(4):214.

BACKGROUND: Pulmonary hypertension is characterized by abnormal thickening of the pulmonary arteries and increased pulmonary vascular resistance. Nitric oxide is a potent endothelium-derived vasorelaxant substance and an inhibitor of smooth-muscle-cell growth. Nitric oxide is produced in various cell types by the action of an enzyme, nitric oxide synthase. We compared the expression of endothelial nitric oxide synthase in the lungs of control subjects with that in the lungs of patients with pulmonary hypertension. METHODS: We investigated the expression of endothelial nitric oxide synthase by histochemical and immunohistochemical analysis, in situ hybridization, and Northern-blot analysis in the lungs of 22 patients with plexogenic pulmonary arteriopathy (arteriopathy of grades 4 through 6), 24 patients with secondary pulmonary hypertension (arteriopathy of grades 1 through 3), and 23 control subjects. RESULTS: In the lungs of the control subjects, nitric oxide synthase was expressed at a high level in the vascular endothelium of all types of vessels and in the pulmonary epithelium. In contrast, little or no expression of the enzyme was found in the vascular endothelium of pulmonary arteries with severe histologic abnormalities (ie, plexiform lesions) in patients with pulmonary hypertension. The intensity of the enzyme immunoreactivity correlated inversely with the severity of histologic changes. There was an inverse correlation between the arterial expression of the enzyme and total pulmonary resistance in patients with plexogenic pulmonary arteriopathy ($r = -0.766$, $p = 0.004$). CONCLUSIONS: Pulmonary hypertension is associated with diminished expression of endothelial nitric oxide synthase. It is possible that decreased expression of nitric oxide synthase may contribute to pulmonary vasoconstriction and to the excessive growth of the tunica media observed in this disease. *See the related editorial: **Nitric Oxide and Vascular Disease**—J Loscalzo. N Engl J Med 1995;333(4): 251-253.*

Outbreak of Tuberculosis among Regular Patrons of a Neighborhood Bar—SE Kline, LL Hedemark, SF Davies. N Engl J Med 1995;333 (4):222.

BACKGROUND: Outbreaks of tuberculosis have been reported in prisons, nursing homes, urban homeless shelters, and other crowded settings. We report a nonresidential outbreak of tuberculosis that originated in a neighborhood bar. METHODS: A homeless patient with highly infectious pulmonary tuberculosis was a regular patron of a neighborhood bar during a long symptomatic interval before diagnosis. We Investigated 97 other regular customers and employees of the bar through interviews, tuberculin skin testing, and chest roentgenography. We performed DNA fingerprinting on isolates from the index patient and 11 other patients. RESULTS: The index patient apparently infected 41 of 97 contacts (42 percent), resulting in 14 cases of active tuberculosis and 27 cases of infection but no disease (indicated by positive tuberculin skin tests). Four other cases of active tuberculosis occurred among regular customers of the bar who were missed by the contact investigation. There were also two secondary cases. Radiographic findings in active cases included upper-lobe disease in seven cases (three cavitary) and negative chest films at the time of diagnosis in four cases. All 12 culture isolates we tested had the same chromosomal-DNA restriction pattern. CONCLUSIONS: The spread of tuberculosis in a neighborhood bar can be a major public health problem. The high rate of infection and disease among the contacts was unexpected and was not due to co-infection with the human immunodeficiency virus. Possible explanations include heavy alcohol use among the contacts, high infectivity of the index case, or both. Sputum cultures must be performed in tuberculin-positive contacts who have symptoms, even if the chest films are normal.

Do Radiographic Criteria for Emphysema Predict Physiologic Impairment?—KH Kilburn, RH Warshaw, JC Thornton. Chest 1995;107(5):1225.

OBJECTIVE: The functional consequences of pulmonary emphysema have been estimated from autopsy studies. This antemortem study correlates structure as assessed by criteria applied to chest radiographs and function in earlier disease SUBJECTS AND METHODS: Four thousand one hundred seven male shipyard and construction workers had chest radiographs scored for asbestosis using International Labour Office criteria and for emphysema using five criteria: hyperlucent lung fields, low flat diaphragms on posteroanterior views, low flat diaphragms on lateral radiographs a wide retrosternal space, and bullae. Total lung capacity (TLC) was measured by planimetry of radiographs and forced vital capacity (FVC) and flows by Spirometry: TLC minus FVC equated residual volume (RV). All were expressed as percentage of predicted (% pred) adjusted for height, age, and duration of cigarette smoking. Linear regression modeling examined the influence of each emphysema criterion on function measurements. RESULTS: Four hundred three (10.1%) of 4,107 men had two or more emphysema criteria and 24.5% had asbestosis. Prevalence of 2 criteria varied by smoking status and was present in 20% of current smokers, 7.5% of ex-smokers, and 2% of never smokers. The TLC % pred and RV/TLC increased and % pred of FEV_1/FVC and FEF^{25-75}, FEV_1, and FVC decreased with increasing radiographic emphysema criteria. Forty-four (10%) had normal results of spirometry with two or more radiographic emphysema criteria. CONCLUSION: Impairment of airway function worsened with each additional radiographic criteria of emphysema. These criteria were more strongly associated with an increase in RV/ TLC than an increase in TLC.

Adherence to Established Guidelines for Preoperative Pulmonary Function Testing—OW Hnatiuk, TA Dillard, KG Torrington. Chest 1995; 107(5):1294.

Guidelines for ordering preoperative spirometry have been proposed by GM Tisi (1979) and more recently by the American College of Physicians (ACP). Requests for preoperative spirometries represent a significant portion of all requests for screening spirometry at our institution and utilize significant man-hours of technician time. We determined the percentage of these requests that did not meet the ACP guidelines and characterized why these requests were being generated. We sampled 441 screening spirometries performed by the Walter Reed Pulmonary Function Laboratory over a 4-week period. One hundred thirty-eight (31%) of these were done preoperatively and complete data were available in 135 cases. Patients in the analyzed group had a mean age of 59 years (± 14 years), ranging from 20 to 84 years of age. Fifty-two (39%) requests did not meet ACP guidelines. Most of these requests were associated with either normal spirometry ($n = 34$) or only mild spirometric abnormalities ($n = 14$). Spirometry revealed severe obstruction in only one case when the request was not indicated. No cases of moderate obstruction, severe restrictive pattern, or possible upper airway obstruction were found in the group of requests in which spirometry was not indicated. Of the requests that did not meet ACP guidelines, 21 met Tisi's broader guidelines. Most of these requests were found exclusively in patients older than 70 years of age ($n = 13$) and the morbidly obese ($n = 4$). Of the 31 studies that did not meet either set of guidelines, 25 occurred in asymptomatic, current, or prior smokers. In conclusion, during a 4-week study period at our institution, 39% of preoperative spirometry requests did not meet ACP guidelines. Most of the patients had been referred because of age greater than 70 years, morbid obesity, and a current/prior history of smoking. However,

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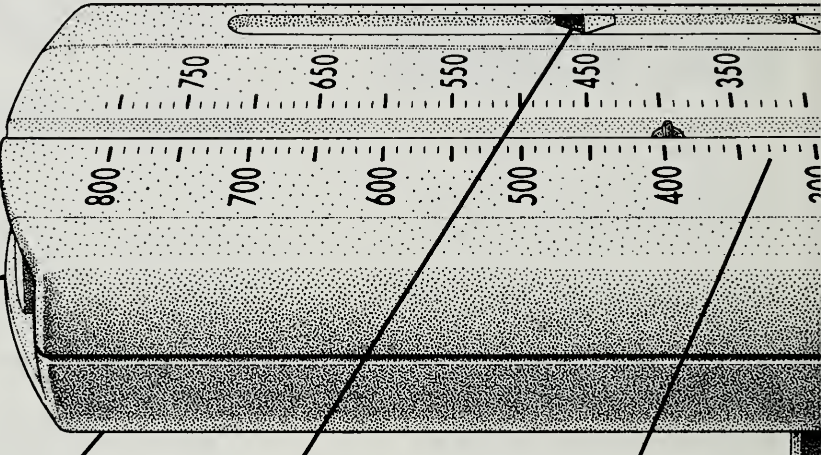

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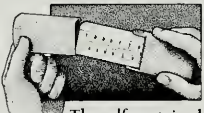

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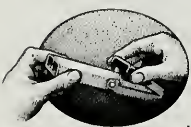

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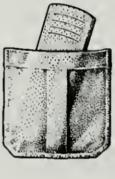

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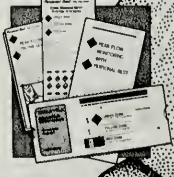

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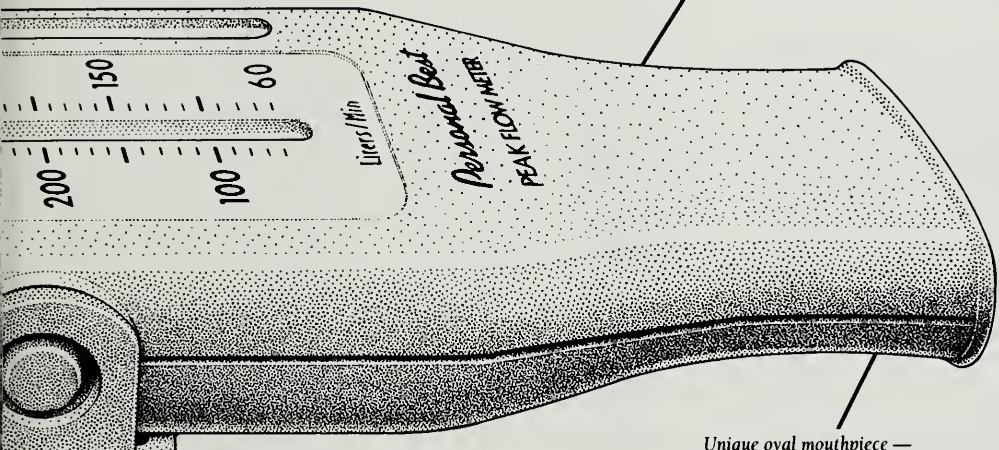

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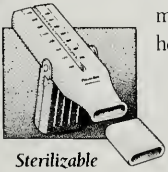

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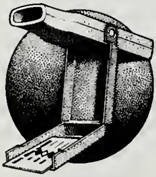

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the literature does not support obtaining preoperative spirometry in such patients except for those undergoing only lung resection. We recommend stricter adherence to the ACP guidelines as a means of decreasing the number and cost of unnecessary spirometries being performed.

Determinants of Mortality and Multiorgan Dysfunction in Cardiac Surgery Patients Requiring Prolonged Mechanical Ventilation—MH Kollef, T Wragge, C Pasque. Chest 1995;107(5):1395.

OBJECTIVES: To identify characteristics associated with mortality and the development of multiorgan dysfunction in patients who had undergone cardiac surgery and required prolonged mechanical ventilation, ie, > 48 h. DESIGN: A prospective cohort study. SETTING: Barnes Hospital, St Louis, an academic tertiary care center. PATIENTS OR OTHER PARTICIPANTS: A total of 107 consecutive patients undergoing cardiac surgery and requiring prolonged mechanical ventilation. INTERVENTIONS: Prospective patient surveillance and data collection. MAIN OUTCOME MEASURES: ICU mortality and multiorgan dysfunction. RESULTS: Among 472 consecutive patients admitted to the cardiac surgery ICU following surgery, 107 (22.7%) required prolonged mechanical ventilation. Twenty-one of these patients (19.6%) died during their hospitalization. In a logistic-regression analysis, the development of an organ system failure index (OSFI) of 3 or greater was the only characteristic independently associated with ICU mortality ($p < 0.001$). The occurrence of an antibiotic-resistant infection (adjusted odds ratio [AOR] = 6.1, 95% confidence interval [CI] = 2.5 to 14.6, $p = 0.006$), an aortic cross-clamp time equal to or greater than 1.25 h (AOR = 3.9, CI = 2.3 to 6.8, $p = 0.016$), the development of ventilator-associated pneumonia (AOR = 3.6, CI = 2.4 to 5.3, $p < 0.001$), and an APACHE III score equal to or greater than 30 (AOR = 3.1, CI = 1.8 to 5.3, $p = 0.036$) were independently associated with the development of an OSFI of 3 or greater. CONCLUSIONS: These data confirm that acquired multiorgan dysfunction is the best predictor of mortality in patients requiring prolonged mechanical ventilation following cardiac surgery. Additionally, they identify potential determinants of multiorgan dysfunction and suggest possible interventions for its reduction in this patient population.

Bronchodilator Subsensitivity to Salbutamol after Twice Daily Salmeterol in Asthmatic Patients—A Grove, BJ Lipworth. Lancet 1995;346 (8969):201.

In view of current concerns about use of regular beta-2 agonists, and the place of the newer long-acting drugs, we decided to evaluate whether continuous exposure to twice daily salmeterol results in a blunting of the acute bronchodilator response to repeated doses of salbutamol, as might be administered in the management of an acute asthma attack. After a 2 week run-in without beta-2 agonists, 17 asthmatic patients (mean [SE] age 34 [3] years, mean forced expiratory volume in 1 s [FEV_1] 64 [2.7]% of predicted) were randomized to receive salmeterol 50 μg twice daily or placebo for 4 weeks in a double-blind crossover fashion. A histamine challenge test was done 12 h after the last dose of each treatment period, and dose-response curves to inhaled salbutamol (200-3200 μg) were constructed 36 h after the last dose. Patients treated with salmeterol had reduced bronchodilator responses to salbutamol in terms of FEV_1 and peak-expiratory flowrate (PEFR) than those treated with placebo. The reduction in response equated with a 2.5-fold and a 4-fold greater dose of salbutamol being required to produce a given FEV_1 and PEFR, respectively. There was a significant reduction in lymphocyte beta-2 adrenoceptor density after salmeterol compared with placebo and run-in. Salmeterol remained effective in terms of disease control, with a significant improvement in morning PEFR compared with placebo that was maintained over the 4 week treatment period. Continuous exposure to salmeterol 50 μg twice daily results in subsensitivity to the acute bronchodilator response to repeated doses of inhaled salbutamol. Thus patients receiving regular treatment with salmeterol might require higher doses of salbutamol when used for relief of acute bronchoconstriction.

Ribavirin Therapy: Implementation of Hospital Guidelines and Effect on Usage and Cost of Therapy—TJ Feldstein, JL Swegarden, GF Atwood, CD Peterson. Pediatrics 1995;96(1):14.

OBJECTIVE: The American Academy of Pediatrics (AAP) recommends that ribavirin be reserved for infants who are severely ill and who are at high risk of morbidity and mortality, based on underlying clinical conditions. The purpose of this study was to evaluate current ribavirin use in our institution, implement hospital-specific guidelines for use, develop a prospective surveillance system to monitor ribavirin therapy, and evaluate the impact of these guidelines on subsequent use and cost of therapy. METHODS: Ribavirin use was compared with the recommendations of the AAP. Results were presented to the professional staff, and hospital guidelines were implemented. Ribavirin therapy was re-evaluated in a 2-year period after hospital guidelines were implemented. RESULTS: In the initial evaluation period, only 67% of the ribavirin recipients met the AAP guidelines for use, and 19% received an inappropriate treatment regimen. The total cost and billed patient charges for ribavirin recipients who did not meet the guidelines for use in period 1 was $60,638 and $127,940, respectively. Over the next 2 years (period 2) after the implementation of hospital guidelines, the percentage of patients who received ribavirin decreased 35%, and approximately 96% of ribavirin recipients met the established criteria. Based on the decrease in the percentage of patients who received ribavirin in period 2 (41% vs 63%), the estimated cost avoidance and reduction in billed patient charges in period 2 was $55,540 and $117,334, respectively. This represents an estimated reduction in hospital costs and billed patient charges of $46,283 and $97,778 per 100 admissions for acute bronchiolitis. CONCLUSIONS: Before the implementation of hospital guidelines for use, a substantial percent of patients received ribavirin not consistent with the recommendations of the AAP. Following the adoption of a modified version of the AAP guidelines for our institution and the use of a multidisciplinary surveillance system for monitoring ribavirin therapy, we observed a substantial decrease in the overall ribavirin use. This has resulted in a significant savings in terms of cost avoidance and reduced billed patient charges.

Reduction in Obstructive Breathing Events during Body Rocking: A Controlled Polygraphic Study in Preterm and Full-Term Infants—J Groswasser, M Sottiaux, E Rebuffat, T Simon, M Vandeweyer, I Kelmanson, D Blum, A Kahn. Pediatrics 1995;96(1):64.

OBJECTIVE: To investigate the effect of body rocking on infant respiratory behavior during sleep. METHODS: Eighteen infants with documented obstructive sleep apneas were studied. There were eight premature infants with persistent bradycardias and 10 infants born full-term, admitted after an idiopathic apparent life-threatening event. No cause for the obstructive apneas was found. The infants were recorded with polygraphic techniques during two successive nights. They were randomly assigned to a rocking or a nonrocking mattress. The conditions were reversed the following night, in a crossover design. RESULTS: In both groups of infants, no significant difference was seen between the two consecutive nights for most of the variables studied: total sleep time, the proportion of non-rapid-eye-movement and rapid-eye-movement sleep, the number of arousals, the number and maximal duration of central apneas, the frequency of periodic breathing, the level of oxygen saturation, and heart rate. During the nonrocking nights, all infants had repeated obstructive breathing events. In seven of the eight preterm infants and in nine of the 10 full-term subjects, body rocking was associated with a significant decrease in the frequency of obstructive events. During rocking, in the preterm infants the obstructions fell from a median of 2.5 to 1.8 episodes per hour ($p = 0.034$). In the full-term infants, rocking reduced the obstructive events from a median of 1.5 obstructions per hour to 0.7 ($p = 0.005$). No difference was seen for the duration of the obstructive episodes. CONCLUSION: In preterm and full-term infants prone to obstructive sleep apneas, gentle side-to-side body rocking is associated with a significant decrease in the frequency of upper-airway obstructions.

Consensus III:
Assessing Innovations in Mechanical Ventilatory Support

This issue of the Journal[1] comprises the Consensus Statement and supporting papers that grew out of the Consensus Conference on "Assessing Innovations in Mechanical Ventilatory Support," sponsored and funded through the American Respiratory Care Foundation and co-sponsored by the American Association for Respiratory Care.

The Consensus Conference, the Consensus Statement, and this Special Issue were 'a long time coming.' The possibility of such a Conference first arose in the course of 'brainstorming' by the Journal's Editorial Board some 5 or 6 years ago, in preparation for the Consensus Conference on the Essentials of Mechanical Ventilators—1992.[2] Details were slow to jell until 1993 when Neil MacIntyre and Tom East began to develop the idea in earnest.

Some of these papers provide the background material (history, if you will), some address general problems, some specific problems. Some aspects are well-documented, whereas others by their very nature are based on opinion and anecdote. One could construe the issue's melody as being primarily an expression of the frustration of manufacturers over the delays and expense of gaining approval from the Food and Drug Administration for new products, with a descant projecting the arbitrary nature of FDA decisions. But, that is far from true, and that construction should not detract from the other messages emanating from those participating. Other themes, important themes, supported both by 'hard' and 'soft' data recur—the absolute necessity for demonstration of safety and effectiveness, the difficulty with and importance of establishing meaningful end points for device testing, the responsibilities of participants to the process.

But where do the Journal and its Editors sit in regard to the publication of material based in part on unsubstantiated opinion and anecdote? First, we must answer the Why questions. The first Why—Why publish such material at all? We have chosen to publish because we believe that it is important to clearly delineate the issues addressed by the Conference and its Consensus Statement. The Consensus Statement is just that—a 'meeting of the minds' of a group who daily in a half dozen or more different ways face the problems of increasing costs, unsafe or ineffective treatment or equipment, questionable end points, and lack of access to potentially valuable applications. The second Why—Why should a peer-reviewed science journal publish unsubstantiated opinion and anecdote—a clear departure from an honorable, long-established position? We chose to do so because it became impossible to project the flavor of the problems, particularly from the manufacturers' point of view without (to change the metaphor) establishing these scenarios. As a Journal editorialist[4] expressed his concerns about work redesign "Do save the baby!" The 'baby' for innovations in mechanical ventilatory support are

- Innovations are needed, and all players—manufacturers, regulatory agencies, clinicians, and payers—have responsibilities to the innovation-assessment process.
- The criteria for efficacy testing should be based on an innovation's risk and cost.
- Payers have a responsibility to insist on assessment criteria consistent with risk and cost.
- Regulatory groups must become more flexible, adopt more realistic criteria for assessment, and streamline the approval process, and legislators must fund in a manner that allows agencies to discharge those responsibilities.
- Professional groups have a responsibility to manufacturers and payers to serve as consultants for and assessors of innovation.

The content and recommendations of this Special Issue have importance for all of us—citizens, clinicians, manufacturers, regulators, and payers alike.

Pat Brougher
Editor
RESPIRATORY CARE

REFERENCES

1. MacIntyre NR, East TD, editors. Assessing innovations in mechanical ventilatory support.(special issue). Respir Care 1995;40(9):968-970.
2. MacIntyre NR, Branson RD, editors. The essential of mechanical ventilators (special issue). Respir Care 1992;37(9):961-1136.
3. Hess D, Branson RD Case studies on mechanical ventilator innovations: perspectives of two clinicians. Respir Care 1995;45(9): 957-967.
4. Stoller JK. Respiratory care in the era of work redesign: out with the bath water (maybe) but do save the baby (editorial). Respir Care 1995; 40(7):700-701.

Consensus Conference III: Assessing Innovations in Mechanical Ventilatory Support

A Special Issue

containing the papers and Consensus Statement from
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American Respiratory
Care Foundation

Consensus Conference:
Assessing Innovations in Mechanical Ventilatory Support

Preamble

Objective

Mechanical ventilation systems have provided sophisticated life support technology for millions of patients during the last five decades. Despite this success, important clinical limitations, serious potential hazards, and high costs remain associated with these systems. Innovations, both in device design and device application, that address these issues are clearly needed, and their development should be encouraged.

The process of bringing innovations to the clinical arena is a complex one that is heavily influenced by developmental and implementational cost factors, reimbursement potential, and regulatory issues. In the end, safety and efficacy must be demonstrated to regulatory bodies, clinicians, and payers before an innovation is put into practice. Establishing efficacy, however, can be problematic. In an effort to minimize the development costs, manufacturers often seek to establish efficacy using relatively inexpensive approaches, such as clinician-preference surveys, lung-model engineering studies, and crossover studies with physiologic end points. However, clinicians (and payers) need to be sure that innovations provide a better outcome for their patients and are worth the associated anticipated risks or extra costs. This may require randomized, controlled trials (RCTs) with clinically important end points. Such trials, however, are complex and expensive because changes in outcome (eg, survival) that might be expected from improvements in existing support technology are likely to be small (although important), and, thus, difficult to detect in patient populations in which ultimate outcomes are determined by a host of other factors.

The purpose of the Consensus Conference was to put efficacy assessment for innovations in mechanical ventilation into a perspective based on risks and costs. The specific goals were threefold: First, we wanted to state that there are important limitations to current mechanical ventilation systems that may be improved through innovation. Second, we wanted to describe the problems encountered in developing innovations—from idea to product to market—from the perspective of manufacturers, clinicians, and regulators. Third, we wanted to provide a framework for efficacy assessment that utilizes an expeditious technical and/or physiologic efficacy assessment for low-risk/low-cost innovations but mandates properly controlled clinical trials with relevant outcomes for high-risk/high-cost innovations.

Participants

Fourteen participants were selected to present the issues facing manufacturers, clinicians, regulators, and payers. The participants included physicians, engineers, and respiratory therapists with expertise in mechanical ventilators, the regulatory process, manufacturing principles, marketing, and reimbursement issues.

These participants gave formal presentations addressing specific issues, with considerable discussion following each. Eight manufacturers had observers present for all discussions, and representatives of three of those manufacturers were invited to participate in a round-table discussion at the end of the Conference. The Conference was underwritten by unrestricted educational grants to the American Respiratory Care Foundation from the eight manufacturers.

Evidence

The 14 presentations and subsequent discussions constituted the evidence. These presentations were given over a 2-day period and are published elsewhere in this issue. Topics included:

- The limitations of current mechanical ventilator systems
- Innovation development—the manufacturer's perspective
- Innovation development—the clinician's perspective
- Innovation development—the regulatory perspective
- Case studies in product development
- Physiologic end points to assess efficacy
- Clinical-outcome end points to assess efficacy
- Statistical concerns in efficacy assessment
- Funding innovation development
- A framework for assessing efficacy based on risks and costs

Consensus Process

The writing committee devised a framework for the Consensus Statement. The key topics were determined before the Conference and included:

- The need for innovation
- The process of developing innovations—responsibilities of manufacturers, clinicians, regulators, and payers.
- Criteria to assess innovations—engineering versus physiologic versus clinical-outcome end points.
- Problems with the current system of introducing innovations—the perspective of manufacturers, clinicians, regulators, and payers.

Recommendations

Throughout all the presentations and discussions, members of the writing committee assigned to each key topic attempted to capture the sense of consensus in their written summary of that topic. On the last day of the Conference, a draft of the summary was distributed to all participants for open discussion. A preliminary consensus on the spirit of the draft was obtained through these discussions. Successive drafts were circulated to all participants and modified during the next 4 months, until all could support the Consensus Statement.

Consensus Statement: Assessing Innovations in Mechanical Ventilatory Support

I. Innovations Are Needed

Although positive-pressure mechanical ventilation has provided successful respiratory support for millions of patients, and now has greater capabilities for the delivery and monitoring than at any time in the past, innovations are still needed. Aspects of mechanical ventilation where innovations are needed include:

- Improving ventilator-support capabilities, especially in very ill patients in whom gas exchange goals can be difficult (or impossible) to achieve;
- Reducing complications related to mechanical ventilation, especially the cardiovascular effects of positive intrathoracic pressure; dynamic hyperinflation and auto-PEEP; ventilator-induced lung injury; and complications related to intubation, artificial airways, and tracheostomy.
- Improving many issues affecting the clinician-user, including standardization of terminology, definitions, and labeling; simplification of controls, options, and displays; versatility in adaptation to varying patient needs; clinically relevant monitoring, both in the functions assessed and in how monitors function; and standardization and increased clinical relevance of alarms.
- Improving many issues affecting the patient, especially patient comfort during interactive ventilator support, and patient safety.
- Reducing costs.

Innovations to address these and other issues are clearly needed and could range from simple software changes that improve the manipulation of air flow to radically different concepts in respiratory support, such as liquid ventilation.

II. The Process of Innovation Development

Bringing an innovative concept related to mechanical ventilation to clinical reality is a complex process. Four distinct groups interact in this process, each with its own responsibilities and concerns:

1. Manufacturers have the responsibility to build the device in accordance with good manufacturing practices (GMP). It is usually also the manufacturer's responsibility to perform the testing that establishes safety and efficacy. From the manufacturer's perspective, direct development costs (including the cost of assessing efficacy), education/manufacturing costs, and liability concerns must be balanced against the potential profitability of the innovation.

2. Regulatory agencies have the statutory responsibility to assure safety and efficacy before allowing an innovation to be marketed. Moreover, regulatory agencies must assure that device labeling and advertising are consistent with the claims that have been validated. These responsibilities apply both to new devices and to new claims by manufacturers for uses of existing devices. Regulatory agencies must balance the dual responsibilities of allowing expedient approval of helpful innovations and denying approval of harmful or unhelpful innovations.

3. Clinicians have the responsibility to use safe and effective innovations in the treatment of their patients in an effort to improve clinical outcome. This clinical outcome may be an ultimate outcome (eg, improved survival, decreased length of hospital stay), a patient-management outcome (eg, increased comfort, less noise), or a cost outcome. A clinician-initiated innovation (ie, device application outside the approved labeling) places additional responsibilities on the clinician. Specifically, the clinician has the responsibility to generate safety and efficacy data for that application before widespread clinical use and accompanying liability protection can be justified.

4. Payers have the responsibility to assure that the benefits of the innovation are sufficient to justify their costs before widespread reimbursement is appropriate.

III. Efficacy Assessment Criteria

Efficacy assessment is the demonstration that an innovation does what is claimed. Efficacy is generally assessed in a controlled study and must be distinguished from effectiveness, which implies usefulness in the uncontrolled clinical environment. Effectiveness can be established only after efficacy has been ascertained and is a complex process beyond the scope of this document.

The three basic approaches to assessing the efficacy of an innovation in mechanical ventilatory support are shown in Table 1: **(1) Engineering testing:** This involves evaluating and verifying design specifications in a suitable testing laboratory, or in an animal/clinical situation. **(2) Physiologic testing:** This involves evaluating pertinent clinical or physiologic responses (eg, gas exchange, lung mechanics) in a relevant population. **(3) Outcome testing:** This involves evaluating overall outcome such as survival, iatrogenic injury, or days alive and off mechanical ventilation in a relevant population. These three approaches to assessment differ in their cost, their complexity, and their potential for defining efficacy.

Table 1. Examples of Types of End Points for Efficacy Assessment in Mechanical Ventilation

Level I	Engineering Assessment – Valve performance (sensitivity, responsiveness) – Monitor accuracy – Flow capabilities – Ease of operation – Noise – Durability – Cost of operation
Level II	Physiologic Assessment – Ventilation (total, alveolar, dead space) – Gas exchange – Cardiac function (filling, contractility) – Respiratory system mechanics – Muscle function (drive, work, pressure-time products) – Air trapping (intrinsic PEEP)
Level III	Clinical-Outcome Assessment – Overall survival, long-term survival – Ventilator days, ICU days, hospital days – Days alive off ventilator – Incidence of important complications (barotrauma, pneumonia)

Laboratory, animal, or clinical studies assessing engineering specifications (eg, trigger sensitivity) are relatively inexpensive, and the results are generally related directly to the device. However, because of the limitations of engineering-focused studies, results usually cannot be used to predict changes in clinical outcome.

Evaluations using intermediate physiologic end points are more expensive because a formal clinical study is required (eg, crossover study, case-control study). Ideally, physiologic end points should be chosen both because they have relevance to the innovation's claimed benefit/potential risk, and because these variables are reasonably linked to a clinical outcome. Nevertheless, because these physiologic variables are only surrogates for patient outcome (eg, survival, hospital length of stay) the real impact of the innovation on actual outcome can only be inferred.

Finally, clinical outcome studies are the most focused on ultimate benefits but are also the most complex and expensive studies to perform. Although several study designs lend themselves to assessment of clinical outcome, the randomized, controlled trial (RCT) is probably the best. This is because end points can be chosen that are clinically important and objective and because the process of randomization reduces bias that may occur when investigators choose the recipients of the treatment under consideration. Survival is often used as an end point in RCTs designed to assess medical therapies. However, a mechanical ventilator is a support device, not a therapeutic device. An impact on survival may thus be difficult to show in patients in whom many more important factors than just the support device affect survival. More device-focused but clinically important end points may be complication rates, ICU length of stay, or ventilator-free days. Another issue in the design of an RCT is patient selection. To improve the validity and power of an outcome study, designers may constrain the study to a specific population. This, however, leads to difficulties in generalizing the results to other patients. A final issue is sample size. Planning the sample size in an RCT depends on the expected impact of the innovations and on the baseline variability of the selected end point(s) in the study population. Large and expensive studies may thus be necessary to reduce the chance of missing small benefits in a population that has considerable variability. These cases must be balanced against the potential cost of using expensive technology of unproven benefit.

Uncontrolled, nonrandomized clinical observations have only a limited role in assessing clinical outcome. This type of evaluation has utility in that it is often inexpensive, can include a broad range of patients, and can evaluate multiple therapies. Nevertheless, these evaluations are subject to bias and confounding with respect to patient selection, severity, and case-mix. Conclusions about the causal relationship between treatment and outcome are much weaker than in an RCT. Uncontrolled studies thus have a limited role in establishing efficacy, although a negative study can be evidence against a claimed benefit.

Table 2 Specific Problems Associated with Assessing Innovations

From the manufacturer's perspective
- Efficacy criteria required for regulators, payers, and clinicians are often unclear (ie, What needs to be demonstrated?).
- Regulatory process is viewed as overly cautious and slow.
- Establishing efficacy is a costly portion of innovation development.

From the regulatory agency's perspective:
- Federal mandates for ensuring public protection from harmful devices requires more regulation and a less speedy approval process.
- Mechanical ventilation innovations are increasingly complex—especially microprocessor systems and software.
- Efficacy criteria for medical devices are not well established (ie, Which devices need only engineering tests or 510(k) review and which devices need physiologic or clinical outcomes tests or pre-market application review?).
- Federal funding to perform an increasingly complex task is shrinking.

From the clinician's perspective:
- Claims by an innovation's advocate may not be supported by appropriate levels of efficacy assessment (ie, physiologic claims are made from engineering tests and outcome claims are made from physiologic tests); Clinicians must realize that the freedom to use devices beyond established applications must be balanced by safety, liability, and reimbursement concerns.
- Manufacturers, regulators, and payers can be perceived as being too slow in making innovations possible.

From the payer's perspective:
- Cost analyses of innovations are rarely done.
- Definitions of 'beneficial' cost-effectiveness to justify reimbursement do not exist for mechanical ventilation innovations.

IV. Problems with the Current System for Assessing Efficacy.

A number of problems are associated with assessing efficacy for innovations in mechanical ventilation. In general, these problems arise from the need to balance three, often-conflicting goals: rapid introduction of safe and effective innovations, blocking of harmful or useless innovations, and containment of all aspects of health care costs. Specific problems facing manufacturers, regulators, clinicians, and payers are given in Table 2.

IV. Recommendations

A. Establish efficacy criteria based on an innovation's risk and cost. Specifically (Table 3):

1. Regulatory agencies and clinicians should require efficacy assessment at a level commensurate with the anticipated risk that the innovation may add to mechanical ventilators. A reasonable three-level risk-specifications scheme would be:

minimal or minor risk:	harm unlikely
moderate risk:	harm possible, mortality unlikely to be affected
major risk:	harm possible, mortality mortality may be affected

Claims for devices that have *minimal* anticipated risk would require an assessment validating engineering specifications. Claims for devices that have *moderate* anticipated risk would require studies using physiologic end points. Claims for devices that have a *major* anticipated risk would require an assessment using clinical outcome end points.

Table 3. Efficacy Criteria Required for Innovations*

		Incremental Cost Increase (Payer Issues)		
		Minor	Moderate	Major
Incremental Risk Increase (Regulatory/ Clinician Issues)	Minor	Level I	Level II	Level III
	Moderate	Level II	Level II	Level III
	Major	Level III	Level III	Level III

*Level I = Engineering end points, Level II = Physiologic (intermediate) end points, Level III = Clinical outcome end points.

2. Payers should, in addition to requiring assessment commensurate with risk, require efficacy assessment at a level also commensurate with the incremental cost (ie, the annual amortized life-cycle cost) that the innovation may add to mechanical ventilation. This may require a higher level of assessment than that needed to satisfy regulatory agencies. An example of a three-level incremental cost-stratification scheme would be:

minimal or minor cost:	less than 1% of a respiratory care service (RCS) budget
moderate cost:	1-5% of an RCS budget
major cost:	more than 5% of an RCS budget

   Efficacy assessment focused on engineering design features would be reasonable only for minimal cost innovations. Efficacy assessment focused on physiologic effects would be required for moderate cost innovations. Efficacy assessment focused on clinical outcome would be required for a high cost innovation.

B. Regulatory bodies need more flexibility to apply these criteria appropriately and with a minimal amount of paperwork and bureaucratic delay. Federal funding should be commensurate with workload. Regulatory bodies should remember that approving safe and useful innovations can be as important to public health as preventing the manufacture of harmful or ineffective ones.

C. Professional organizations should form groups to serve as consulting resources for manufacturers and third-party payers' assessing innovations.

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Current Limitations of Mechanical Ventilation: What Improvements Should the Clinician Expect?

David J Pierson MD

I. Mechanical Ventilation: Is the Ideal a Reasonable Goal?
II. The Evolution of Mechanical Ventilation
III. Current Limitations & Areas for Innovation
  A. Ventilator Capabilities
  B. Ventilator-Associated Complications
  C. Issues Affecting the Clinician
    1. Standardization
    2. Simplifications
    3. Versatility
    4. Monitoring
    5. Alarms
  D. Issues Affecting the Patient
  E. Issues Pertaining to Costs
IV. In Conclusion

Mechanical Ventilation: Is the Ideal A Reasonable Goal?

My charge in addressing this topic is to identify ways in which the design, operation, and clinical utilization of mechanical ventilators might be improved. It is not difficult to envision a theoretical ideal in this field, and to make a 'wish list' for both ventilators and clinical ventilator management (Table 1). On such a list for the ideal ventilator would be the capability to generate any tidal volume, pressure, or inspiratory flow the clinician might desire, and the ability to produce a limitless array of waveforms, modes, or breathing patterns and to match these perfectly to the needs of the individual patient. This ideal ventilator would be intuitive, easy for clinicians to understand and use (even clinicians with limited training in the principles of physiology and engineering), and acceptable to patients.

Table 1. Mechanical Ventilation: The Ideal

The Ideal Ventilator
- High capability (volumes; pressures; flows)
- Versatile (modes; clinical settings; patient demands)
- Reliable
- Simple to use
- Acceptable to patients
- Inexpensive

The Ideal Mode or Approach to Ventilatory Support
- Meets targets for gas exchange (eg, P_{aO_2}, P_{aCO_2})
- Unloads ventilatory muscles
- Does not compromise cardiac function
- Minimizes exposure to high inspired oxygen tensions
- Does not damage airways or lung parenchyma
- Is intuitive and easy to apply
- Is comfortable for patients
- Facilitates weaning
- Requires minimal monitoring, few laboratory tests
- Is not excessively labor-intensive
- Is inexpensive

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The ideal mode or ventilation strategy would permit attainment of the clinician's chosen arterial blood-gas targets without compromising cardiac function or causing parenchymal lung injury from excessive volumes or pressures. It would minimize exposure to high inspired oxygen fractions (F_{IO_2}), and eliminate the need for translaryngeal or transtracheal intubation, with their attendant predispositions to airway damage and respiratory infections. Like the ideal ventilator, this ideal ventilation mode or strategy would be easy for the clinician to understand and apply, and would be comfortable and acceptable to patients. It would require a minimum of monitoring and would generate a minimum of expense in the form of blood-gas analysis and other laboratory tests.

Like a hypothetical, ideal antibiotic—one that is effective against every known pathogen, does not induce resistance, and, at the same time, causes no adverse effects and is inexpensive to make and administer—all this sounds too good to be true, and it is. No antibiotic could ever fulfill all those requirements, not because the pharmaceutical industry lacks the necessary sophistication to make it, but because some of the individual requirements are mutually incompatible and the combination is inherently impossible. Likewise, to achieve all the attributes of the ideal ventilator or ventilation strategy would not be possible because of the nature of the beast—the inherent limitations created by the human host and its response to disease.

This is not to say that mechanical ventilation cannot move in the direction of perfection. Although not all the items in Table 1 are currently achievable (at least not all at the same time), a number of practical, clinically helpful innovations are within our reach. In this article, I describe a number of directions that such innovations might take. In order to place them in appropriate perspective, I will first refer to the history of ventilators and ventilation strategies during the past quarter century (Table 2).

The Evolution of Mechanical Ventilation

In the early 1970s, the acute respiratory distress syndrome (ARDS)[1] had recently been described,[2] and positive end-expiratory pressure (PEEP)[3] had been identified as an effective means for improving arterial oxygenation in this disorder.[3-5] In use were both pressure-cycled ventilators, such as the Bird Mark 14 and the Bennett PR-2, and volume-cycled ventilators, such as the Bennett MA-1 and the Ohio 560, although they were '97-pound weaklings' in comparison with the ICU ventilators introduced since 1990.[6-8]

The mortality of ARDS was high—about two thirds of the patients died[2]—and clinicians felt the need for more powerful ventilators and more effective management strategies. Both clinician-investigators and a rapidly expanding industry responded vigorously and creatively to this perceived need, and during the succeeding two decades a large number of innovative approaches were put into clinical use (or at least contemplated) for the management of severe respiratory failure[9-11] (Table 3[12-62]). The design and manufacture of ICU ventilators burgeoned in the face of clinician demands for more modes and machine capabilities. Ventilators and their associated monitors and ancillary features became more potent and more versatile—and also much more expensive. Mechanical ventilation became enormously profitable—for the industry, for hospital respiratory care departments, and for the increasing numbers of pulmonologists and anesthesiologists practicing in this field.

Table 2. Evolution of Ventilatory Management in Severe Acute Respiratory Failure

Era	Characteristics of Mechanical Ventilation	Problems
1960s	Limited support capabilities (minute ventilation; flows; pressures)	Available support inadequate for some patients
	Limited monitoring of patient and apparatus	Limited data for appropriate and timely decision making
1970s, 1980s	Greatly increased support capabilities	Ventilator-induced lung injury; increasing costs; fear of litigation
	Greatly increased monitoring capabilities; proliferation of cardiorespiratory variables and clinical indices	Conflicting approaches, goals, and philosophies; absence of controlled trials and outcome data
1990s	Focus on limiting lung exposure to high volumes and pressures (permissive hypercapnia)	Limited resources; risk management
	Focus on decreasing costs and resource use in monitoring	Absence of data on safety; lack of consensus on goals

Although the more exotic approaches listed in Table 3 remain the province of investigators and have seen limited application in clinical practice, during the 1970s and early 1980s the management of patients with ARDS became more aggressive as ventilators of higher capacity were introduced (Fig. 1).[63] The use of PEEP, commonly to levels exceeding 10-15 cm H_2O, in order to keep patients' arterial P_{O_2} values in the normal range, and of 12-15 mL/kg tidal volumes (twice the normal, 'physiologic' values) became the standard of care. Peak airway pressures over 50 cm H_2O, and minute ventilations of more than 20 L/min, were required not infrequently in managing patients with ARDS in order to 'normalize' arterial P_{CO_2}.

With new ventilators and modes came new monitors and new variables for monitoring. The pulmonary artery catheter became an accepted part of the management of critically ill patients and opened up a whole new field of aggressive hemodynamic manipulation, based on calculated indices of oxygenation and management goals not previously familiar to clinicians. Management became more and more complicated, and the costs of ICU care mushroomed—eventually exceeding 1% of the U.S. gross domestic product (GDP).[64] The mortality of ARDS remained about 60%.[65,66]

Table 3. Past and Proposed Innovations in Mechanical Ventilation To Improve Gas Exchange (Chiefly Oxygenation)

- 'Conventional' Ventilator Manipulations[12,13]
  - PEEP,*[3,4] Super-PEEP,[14,15] Optimum PEEP,[16] the systematic PEEP trial[17,18]
  - Variations in pressure-flow waveforms[13] (eg, decelerating flow[19])
  - Inverse I-E† ratio ventilation[20,21]
- New Ventilator Modes or Techniques[22-24]
  - Pressure-targeted ventilation (eg, pressure control[25])
  - Airway pressure release ventilation[26,27]
  - Proportional assist ventilation[28,29]
  - High-frequency ventilation[23,30]
    - High-frequency positive-pressure ventilation
    - High-frequency jet ventilation[31]
    - High-frequency oscillatory ventilation[32]
    - High-frequency body surface oscillation
  - Tracheal gas insufflation[33,34]
  - Differential lung ventilation[35]
- Non-Airway or Supplementary Approaches[36]
  - Extracorporeal membrane oxygenation (ECMO)[37]
  - Low-frequency positive-pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO$_2$R)[38-40]
  - Intravascular oxygenation (IVOX)[41,42]
- New Strategies for Manipulating Oxygen Delivery and Utilization[43]
  - Optimizing O_2 delivery[44-49]
  - Reducing O_2 consumption (eg muscle relaxation; hypothermia)[43]
- Miscellaneous Approaches
  - Prone positioning[50-52]
  - Pharmacologic agents
    - Corticosteroids[53]
    - Prostaglandin E_1[54]
    - Inhaled nitric oxide[55-59]
  - Liquid ventilation; partial liquid ventilation[60-62]

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* PEEP, positive end-expiratory pressure

† I-E, inspiration:expiration

During the 1980s, along with the dozens of articles extolling new devices, modes, and management approaches, reports of a darker side of mechanical ventilation began to appear—ventilator-induced lung injury.[65-70] By 1990, an ever-increasing body of data from both animal models and patients was available to support the notion that repetitively stretching the lung, with high peak volumes and high trans-alveolar pressures, was injurious,[71-74] and a ventilator strategy dedicated to providing whatever pressures and volumes were necessary to maintain normal blood-gas values began to seem less and less advisable. At the same time, several investigators reported that ventilating patients with status asthmaticus[75,76] or ARDS[77-79] at much lower pressures and minute volumes—despite the high P_{CO_2} and lower pH values that this produced—was not only well tolerated but also appeared to decrease mortality. Although no randomized control trials of the new "lung-protective" strategy[10,11,68] (permissive hypercapnia[80-84]) in ARDS have yet appeared, ventilatory management has taken an abrupt turn toward this approach.

Coincident with the emergence of the 'less is more' concept of permissive hypercapnia has come an economic and organizational revolution in U.S. health care, aimed, primarily, at making it less expensive. The days of unlimited reimbursement to hospitals and physicians for new, more expensive management strategies are now gone and with them much of the impetus for innovation in mechanical ventilation. Intensive care units, which account for only 7.5% of U.S. hospital beds but generate 28% of all acute hospital charges,[64] have come under increasing scrutiny as targets for cost reduction.

Yet areas remain in which improvements could benefit both patients and clinicians. In the pages to follow, I describe some of these areas, based on my own observations and biases but also on discussions with a number of respiratory care practitioners whose experience and insights I value.

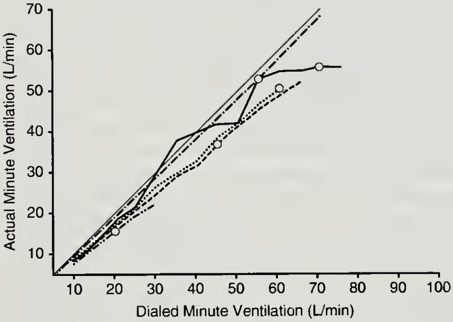

Fig. 1. Performance of four ventilators available in the 1980s [Siemens Servo 900C (—); Puritan-Bennett 7200a (· – ·); Bear 5 (- - -); and Hamilton Veolar (· · · ·)] in comparison with a representative ventilator from a decade earlier [Puritan-Bennett MA-1(· · – · ·)]. Actual delivered minute ventilation (vertical axis) was compared to dialed minute ventilation (horizontal axis) using a test lung. The test conditions were tidal volume 1.00 L, compliance 20 mL/cm H_2O, and PEEP 20 cm H_2O. Circles represent the maximum minute ventilation each ventilator could achieve with inspiratory time less than expiratory time; above the minute ventilations indicated by the circles, I:E ratio became > 1.0. (Reproduced, by permission, from Pierson DJ, Capps JS, Hudson JD: Maximum ventilatory capabilities of four current-generation mechanical ventilators. Respir Care 1986;31:1054-1058.)[63]

Current Limitations & Areas for Innovation

Of all the patients who develop ARDS and who fail to survive the hospitalization, only a minority (approximately 15%) die of ARDS. Most of them die of the underlying illness predisposing to the development of ARDS or as a result of sepsis or other complications.[65,85] Nonetheless, there remain some patients in whom adequate arterial oxygenation cannot be achieved with conventional ventilators and approaches. Patients who require mechanical ventilation for any reason are subject to a host of complications,[86-88] many of which can increase mortality and morbidity. As technologically splendid as current ICU ventilators are, their safe operation and optimal adaptation to patient demands[89] remain difficult and confusing for many clinicians. As a result, patients may experience unnecessary dyspnea and agitation. And, the high costs of purchase, operation, maintenance, and repair constitute a problem not only for respiratory care department managers but also for society as a whole. Thus, there is plenty of room for improvement. The directions that such improvement could take are listed in Table 4 and separated into 5 categories—ventilator capabilities, complications, clinician issues, patient issues, and costs.

Table 4. Aspects of Mechanical Ventilation for which Innovation Would Be Helpful

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Ventilator Capabilities
- (Minute ventilation; inspiratory flows; pressures)
- More clinically relevant monitors

Avoidance of Complications
- Ventilatory support without translaryngeal or transtracheal intubation
- Improved ability to detect risk for or presence of barotrauma
- Detection and warning of inappropriate settings
- Improved reliability

Aspects Affecting the Clinician
- Standardization
  - Terminology
  - Definitions
  - Alarms
- Simplification
  - Number of available waveforms, modes, and variations
  - Number of individual controls and displays
- Versatility and adaptability
  - With different sized patients
  - With varying needs for volume, pressures and flows
  - Ventilator should assist clinician in determination of best settings for each patient (eg, least work of breathing, best compliance, least tachypnea)
- Monitoring
  - More relevant measures of traditional variables
    - Corrected (instead of dialed) tidal volume
    - Plateau (instead of peak) pressure
    - Pressures at airway opening (instead of at exhalation valve)
  - Additional clinically relevant variables
    - Auto-PEEP*
    - Work of breathing (total; ventilator; patient)
    - Lung volumes (eg, FRC,† or at least changes in FRC)
  - Capability of retrieving recent data as needed (eg, trends over several hours), but not necessarily displaying it continuously
  - Capability of detecting clinically inappropriate data (eg, end-inspiratory plateau pressure in actively exhaling patient)
- Alarms
  - Distinctive sounds and/or patterns for alarms indicating different functions
  - Standardization of alarm sounds/patterns among models/manufacturers
  - Improved capability to distinguish between artifact and clinically important change

The Patient-Ventilator Interface
- Better detection and display of failure to meet flow/volume needs
- Better matching of flow and/or volume to patient's needs
- Fewer, less irritating alarms
- Quieter ventilator operation

Cost Considerations
- Motivation/incentives for manufacturers, hospitals, and individual clinicians to reduce costs and choose less resource-intensive therapies
- Protection of individual clinicians, hospitals, and manufacturers from the threat of litigation, while assuring reasonable patient safety

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* PEEP, positive end-expiratory pressure

† FRC, functional residual capacity

Ventilator Capabilities

Is there a need for larger delivered tidal volumes, faster rates, higher pressure capabilities, and higher flows? As demonstrated in Figure 1, the previous generation of ventilators could effectively deliver volumes requiring flows well in excess of 30 L/min at inspiratory-expiratory ratios less than 1, even in the presence of reduced compliance, high levels of PEEP, and large tidal volumes.[63] All current ICU ventilators can generate peak pressures approaching or exceeding 100 cm H_2O.[7,8,89] Studies on experimental animals have amply demonstrated the ability of much lower pressures than this to cause severe lung damage.[71-74] However, even at acceptable airway pressures and tidal volumes, many ventilators in current use do not deliver an inspiratory flow adequate to prevent dyspnea and excessive patient work, especially transiently at the start of inspiration.[90] Healthy persons generate peak inspiratory flowrates well in excess of those produced by many ventilators just in normal conversation, and the inability to inspire rapidly enough is an important contributor to patient-ventilator dyssynchrony in the presence of dyspnea.

As discussed below, it is not so much the maximum output capabilities or number of individual features, but rather the appropriateness, versatility, adaptability, and responsiveness of today's ventilators that could be improved.

Ventilator-Associated Complications

A large number of adverse effects and complications occur in patients on ventilators.[86-88, 91] The main complications of mechanical ventilation are:

- adverse physiologic effects of positive intrathoracic pressure,
- dynamic hyperinflation and auto-PEEP,
- extra-alveolar air (barotrauma),
- consequences of ventilator malfunction,
- complications of intubation and artificial airways,
- ventilator-associated pneumonia, and
- patient-ventilator dyssynchrony ('fighting' the ventilator).

Although the complications listed here occur with discouraging frequency, it should be emphasized that many of them are *associated with*, rather than *caused by* mechanical ventilation.[88] That is, they develop in patients rendered vulnerable to adverse events by critical illness and the invasive support required for its management.

Another way to think about complications that is helpful in positing potential innovations is to classify them as:

- complications caused by the patient's underlying disease (ie, unrelated to management),
- complications caused by how the clinician chooses to use the ventilator (eg, mode, PEEP level, clinical targets),
- complications caused by the ventilator (eg, design, operation, maintenance), or
- complications related to the need for airway access (eg, consequences of intubation and artificial airways; lower airway colonization with subsequent ventilator-associated pneumonia[92, 93]).

From this list only the last two categories would seem amenable to innovation in ventilator design. However, as suggested in Table 4, design features that improve the clinician's ability to prevent or detect ventilator-induced lung injury or that facilitate the selection of volumes, flows, and breathing rates more appropriate to the patient's needs could reduce complications even when these are not primarily a function of ventilator operation.

Issues Affecting the Clinician

Standardization. The current lack of convention and standardization among ventilator models and manufacturers is confusing, especially for clinicians who come into contact with more than one type of ventilator. For example, does AMV mean assisted mechanical ventilation (assist/control mode) or augmented minute volume? When a patient is receiving 20 cm H_2O of pressure support and 15 cm H_2O of PEEP in pressure-targeted ventilation, is the peak airway pressure 20 or 35 cm H_2O? The answers to these and a number of other questions differ depending on which ventilator one is using. All such terminology and definitions should be standardized.

Simplification. Although the multitude of knobs and possible settings on today's ventilators have been put there for good reason and in response to perceived clinician (ie, consumer) demand, the result is often 'too many notes,' to quote the Emperor in the motion picture, *Amadeus*. Even clinician-investigators specializing in this field and caring for the most critically ill patients do not use all the available options, and the array of choices must be very confusing to infrequent, less-expert users. When setting up one type of ventilator currently used in my hospital, the clinician must select from 7 different inspiratory waveforms. Inasmuch as no studies have been done to evaluate whether inspiratory waveforms make a clinically important difference in a patient's recovery from acute respiratory failure, having 7—or even 2—waveform choices seems excessive and unnecessary.

In a thoughtful essay on the ventilator of the future, East[94] envisioned a much simpler device with fewer—rather than more—knobs and indicators. Especially in this era of cost containment, manufacturers and clinicians are going to have to abandon the concept of having every conceivable feature available on every ventilator. 'Enough' is going to have to replace 'everything,' and 'adequate' may have to replace 'ideal.'

Versatility. Patients who present extreme demands for ventilatory support bring out the limitations in some ventilators. For example, consider the needs of the 120-kg man with multisystem trauma and ARDS, with total ventilation 22 L/min and static respiratory system compliance 12 mL/cm H_2O, compared with those of a comatose 45-kg woman following a sedative overdose, whose ventilation requirement is 4 L/min with compliance 90 mL/cm H_2O. The hospital at which I practice cares primarily for adult patients with acute medical-surgical illness. We seldom ventilate infants, but when we do we are quickly reminded of the suboptimal performance of our ventilators for these patients in this setting. Must we purchase a separate ventilator, to be used less often than once a month, for these occasional patients?

Ventilators should not only be able to provide support for patients fitting these descriptions and others, but they should also assist the clinician in determining the best settings for the individual patient. Relevant data to facilitate determination of the most appropriate tidal volume (for example, using compliance and end-inspiratory plateau pressure), flowrate (assessing patient effort and capability), F_{IO_2} and cycling frequency (based on rapid assessment of gas exchange) could reduce clinician time and laboratory utilization as well as patient discomfort.

Monitoring. For understandable reasons, ventilators often monitor what is convenient to monitor rather than what may be most appropriate physiologically. I acknowledge the difficulties involved, but it would be more useful to clinicians to follow corrected tidal volume than dialed volume, more relevant to monitor pressures at the airway opening (or even in the trachea) than at the exhalation valve, and more pertinent to measure plateau pressure than peak inspiratory pressure.

No aspect of ventilator management is more important than the understanding, recognition, and management of auto-PEEP,[95,96] and all ventilators should be capable of monitoring it. Another function crucial to appropriate ventilator adjustment is work of breathing by both ventilator and patient.[90] Some clinically appropriate aspect of the work of breathing should be monitored, especially when modes or approaches providing only partial ventilatory support are used. In addition, the capability of continuously or repeatedly monitoring lung volume (ie, functional residual capacity), or changes in lung volume with changes in PEEP or other therapy, would greatly facilitate management, as this can be a direct measure of the progression of disease and the success of management.[97]

Ventilators should monitor more but display less. My car's dashboard has a digital display that reads 'normal' unless something goes wrong. It does not continuously display the oil pressure, or the function of the brake lights, or whether all the doors are closed. Instead, it keeps track of these things and only tells me about them when the data fall outside the specified monitoring parameters. I believe that it would be of great benefit to patients and the majority of clinicians if ventilators did the same.

With the need for attention to risk management, the ability to retrieve monitoring data, say for the 6 hours preceding an adverse event, would be helpful. Such retrieval could be triggered automatically if the functions being monitored fell outside a set range, but the reams of data collected would not otherwise need to be saved.

Finally, it would be of great help to those managing mechanical ventilation if aberration and artifact could be distinguished from physiologically appropriate measurements. For example, measurements of end-inspiratory plateau pressure or auto-PEEP are not helpful if the patient is actively exhaling, and if this could be detected and indicated by the ventilator (or better yet not accepted as routine monitoring data), there would be less likelihood that inappropriate clinical decisions would be made on the basis of the measurements.

Alarms. Alarms for the same functions on different ventilators have different sounds or patterns, and standardization between models and among manufacturers is badly needed. The same sound should always mean the same thing, regardless of what mode or ventilator is being used.

Innovations are badly needed to reduce the number of nuisance alarms in the ICU. In one recent study of alarms in a pediatric unit, there were 17 false alarms for every true alarm; for ventilator alarms, the positive predictive value (the likelihood that a condition for which the alarm was intended was actually present) was only 3%.[98] There must be ways to distinguish more effectively between an artifact and a clinically important event. Caregivers and patients alike would benefit from an innovation that accomplishes this.

Issues Affecting the Patient

Several of the issues discussed previously have direct impact on the patient's experience of mechanical ventilation. The ideal ventilator should be capable of detecting failure to meet the patient's flow and/or volume needs, and of correcting this automatically, or at least guiding the clinician in doing so. From the patient's standpoint there should be fewer, less irritating alarms[99]—perhaps more use of time delays and remote as opposed to bedside audible alarms except when a caregiver is actually at the bedside, as determined by bedside pressure or motion detectors. Some ventilators make excessive amounts of noise and reducing this would surely be appreciated by patients and caregivers alike.

Issues Pertaining to Costs

Two innovations are badly needed here, although I confess to a lack of ideas for bringing them to fruition. The first is to completely reverse the market forces that have driven ventilator design for 20 years. That is, there must be an appropriate incentive to make less expensive ventilators with fewer features. A decade ago, one of the major ICU ventilators was touted as a basic, relatively inexpensive unit onto which more features could be added if needed, effectively enabling the purchaser to customize and upgrade the product according to the patient population served and other considerations. One could order the 'Rolls Royce' version if one managed lots of high-demand ARDS patients and wanted all the latest features, but a much less expensive 'Chevrolet' version in most other settings.

What happened to that concept? The only versions of that ventilator I have ever seen in actual use are 'Rolls Royces.' It appears that nobody bought 'Chevrolets.' Actually, it's easy to understand what happened. Clinicians wanted all the latest modes and capabilities and monitors, administrators were anxious to say their hospitals had the best available equipment, and the manufacturer could make higher profits by selling top-of-the-line models. None of these things is dishonorable or nefarious. However, this whole process must change if the costs of ventilator management are to be reduced. As I noted earlier and although we may not like it, 'enough' is going to have to replace 'everything,' and 'adequate' may have to replace 'ideal.' Few of us drive Rolls Royces, yet we somehow manage to get to where we need to go.

This is not to say that everyone involved in mechanical ventilation should not continue to strive to make it better. Innovation is as important in the 1990s as it was in the 1970s and 1980s; but the rules are changing, and it is becoming more difficult to place innovations into the process. A sound rationale or some short-term physiologic change without overall outcome or cost-effectiveness data will no longer suffice to justify the introduction of more costly modes or features.

The second cost innovation requires that our culture's behavior change with respect to litigation. If those who deliver health care are to be required to provide less than what could possibly be provided irrespective of expense and resources, then they must be protected from the threat of malpractice suits. At the same time, safeguards must be in place to protect patients from negligence. I cannot envision a workable combination of these things without fundamental changes in our legal system.

In Conclusion

Mechanical ventilation has evolved in such a manner as to maximize the utilization of resources. Now, confronted by the finite nature of those resources, everyone involved with this aspect of respiratory care will have to make adjustments. In what has been intended as a hopeful (if sobering) article, I have tried to suggest ways in which ventilators and ventilatory management might be improved. The challenge of accomplishing at least some of these improvements without further increasing the utilization of resources is a daunting one, but, I hope, not beyond our capabilities.

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REFERENCES

1. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3, Part 1):818-824.
2. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319-323.
3. Pierson DJ, Kacmarek RM. Positive end-expiratory pressure: state of the art after 20 years. Respir Care 1988;33(6, 7):419-501, 539-637.
4. Petty TL, Nett LM, Ashbaugh D. Improvement in oxygenation in the adult respiratory distress syndrome by positive end-expiratory pressure (PEEP). Respir Care 1971;16(4):173-176.
5. Kacmarek RM, Petty TL. Historical development of positive end-expiratory pressure (PEEP). Respir Care 1988;33(6):422-431.
6. Colice GL. Historical perspective on the development of mechanical ventilation. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill, 1994:1-35.
7. Kacmarek RM, Meklaus GJ. The new generation of mechanical ventilators. Crit Care Clin 1990;6(3):551-578.
8. Branson RD, Chatburn RL. Appendix: new generation of microprocessor-based ventilators. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill, 1994: 1233-1259.
9. Mechanical ventilation. American College of Chest Physicians consensus conference. Chest 1993;104(6):1833-1859.
10. Marini JJ. New approaches to the ventilatory management of the adult respiratory distress syndrome. J Crit Care 1992;7:256-267.
11. Marini JJ. New options for the ventilatory management of acute lung injury. New Horiz 1993;1(4):489-503.
12. Sassoon CS, Mahutte CK, Light RW. Ventilator modes old and new. Crit Care Clin 1990;6(3):605-634.
13. Kacmarek RM. Management of the patient-mechanical ventilator system. In: Pierson DJ, Kacmarek RM, editors. Foundations of Respiratory Care. New York: Churchill Livingstone, 1992:973-997.
14. Kirby RR, Downs JB, Civetta JM, Modell JH, Dannemiller FJ, Klein EF, Hodges M. High-level positive end-expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 1975;67(2):156-163.
15. Miller RS, Nelson LD, DiRusso SM, Rutherford EJ, Safcsak K, Morris JA Jr. High-level positive end-expiratory pressure management in trauma-associated adult respiratory distress syndrome. J Trauma 1992;33(2):284-290.
16. Suter PM, Fairley HB, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975;292(6):284-289.
17. Maunder RJ, Rice CL, Benson MS, Hudson LD. Managing positive end-expiratory pressure (PEEP): the Harborview approach. Respir Care 1986;31(11):1059-1068.
18. Hudson LD, Weaver LJ, Haisch CE, Carrico CJ. Positive end-expiratory pressure: reduction and withdrawal. Respir Care 1988;33(7):613-617.
19. Al-Saady N, Bennett ED. Decelerating inspiratory flow waveform improves lung mechanics and gas exchange in patients on intermittent positive-pressure ventilation. Intensive Care Med 1985;11(2):68-75.
20. Abraham E, Yoshihara G. Cardiorespiratory effects of pressure controlled inverse ratio ventilation in severe respiratory failure. Chest 1989;96(6):1356-1359.
21. Marcy TW, Marini JJ. Inverse ratio ventilation in ARDS. Rationale and implementation. Chest 1991;100(2):494-504.
22. MacIntyre NR. New forms of mechanical ventilation in the adult. Clin Chest Med 1988;9(1):47-54.
23. Slutsky AS. Nonconventional methods of ventilation. Am Rev Respir Dis 1988;138(1):175-183.
24. Sassoon CS. Positive pressure ventilation: alternate modes. Chest 1991;100(5):1421-1429.
25. Lessard MR, Guerot E, Lorino H, Lemaire F, Brochard L. Effects of pressure-controlled ventilation with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. Anesthesiology 1994;80(5):983-991.
26. Stock MC, Downs JB, Frolicher DA. Airway pressure release ventilation. Crit Care Med 1987;15(5):462-466.
27. Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe respiratory failure. Chest 1991;200(2):460-463.
28. Younes M. Proportional assist ventilation: a new approach to ventilatory support. Am Rev Respir Dis 1992;145(1):114-120.
29. Younes M, Puddy A, Roberts D, Light RB, Quesada A, Taylor K, et al. Proportional assist ventilation: results of an initial clinical trial. Am Rev Respir Dis 1992;145(1):121-129.
30. Froese AB, Bryan AC. High frequency ventilation. Am Rev Respir Dis 1987;135(6):1363-1374.
31. Carlon CG, Howland WS, Ray C, Miodownik S, Griffin JP, Groeger JS. High-frequency jet ventilation. A prospective randomized evaluation. Chest 1983;84(5):551-559.
32. Gluck E, Heard S, Patel C, Mohr J, Calkins J, Fink MP, Landow L. Use of ultrahigh frequency ventilation in patients with ARDS. A preliminary report. Chest 1993;103(5):1413-1420.
33. Nahum A, Ravenscraft SA, Nakos G, Burke WC, Adams AB, Murry TW, Marini JJ. Tracheal gas insufflation during pressure-control ventilation. Effect of catheter position, diameter, and flow rate. Am Rev Respir Dis 1992;146(6):1411-1418.
34. Ravenscraft SA, Burke WC, Nahum A, et al. Tracheal gas insufflation augments CO_2 clearance during mechanical ventilation. Am Rev Respir Dis 1993;148(2):345-351.
35. Parish JM, Gracey DR, Southorn PA, Pairolero PA, Wheeler JT. Differential mechanical ventilation in respiratory failure due to severe unilateral lung disease. Mayo Clin Proc 1984;59(12):822-828.
36. East TD. The magic bullets in the war on ARDS: aggressive therapy for oxygenation failure. Respir Care 1993;38(6):690-704.
37. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmonds LH, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized study. JAMA 1979;243(20):2193-2196.
38. Gattinoni L, Pesenti A, Mascheoni LD, Gallinoni L, Marcolin R, Furmagalli R, et al. Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986;256(7):881-886.
39. Gattinoni L, Pesenti A, Bombino M, Pelosi P, Brazzi L. Role of extracorporeal circulation in adult respiratory distress syndrome management. New Horiz 1993;1(4):603-612.
40. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149(2, Part 1):295-305.

41. Durbin CG. Intravenous oxygenation and CO_2 removal device: IVOX. Respir Care 1992;37:147-153.
42. Zwischenberger JB, Nguyen TT, Tao W, Bush PE, Cox CS, Traber DL, et al. IVOX with gradual permissive hypercapnia: a new management technique for respiratory failure. J Surg Res 1994;57(1): 99-105.
43. Stoller JK. Therapeutic manipulation of oxygen consumption and carbon dioxide production in acute respiratory failure. Respir Care 1993;38(7):769-783.
44. Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. Crit Care Med 1993;21(7):977-990.
45. Shoemaker WC, Appel PL, Bishop MH. Temporal patterns of blood volume, hemodynamics, and oxygen transport in pathogenesis and therapy of postoperative adult respiratory distress syndrome. New Horiz 1993;1(4):522-537.
46. Bishop MH, Shoemaker WC, Appel PL, Wo CJ, Zwick C, Kram HB, et al. Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patients. Crit Care Med 1993;21(1):56-63.
47. Pasquale MD, Cipolle MD, Cerra FB. Oxygen transport: does increasing supply improve outcome? Respir Care 1993;38(7):800-828.
48. Phang PT, Russell JA. When does $\dot{V}_{O_2}$ depend on D_{O_2}? Respir Care 1993;38(6):618-630.
49. Schumacker PT, Samsel RW. Oxygen supply and consumption in the adult respiratory distress syndrome. Clin Chest Med 1990;11(4): 715-722.
50. Douglas WW, Rehder K, Beynen FM, et al. Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis 1977;115:559-566.
51. Langer M, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients: a clinical study. Chest 1988;94(1):103-107.
52. Hess D, Agarwal NN, Myers CL. Positioning, lung function, and kinetic bed therapy. Respir Care 1992;37(2):181-197.
53. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987;317(25):1565-1570.
54. Bone RC, Slotman G, Maunder R, Silverman H, Hyers TM, Kerstein MD, Ursprung JJ. Randomized double-blind, multicenter study of prostaglandin E1 in patients with adult respiratory distress syndrome. Chest 1989;96(1):114-119.
55. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328(6):399-405.
56. Zapol WM, Hurford WE. Inhaled nitric oxide in adult respiratory distress syndrome and other lung diseases. New Horiz 1993;1(4): 638-650.
57. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M, et al. Inhaled nitric oxide in acute respiratory failure: dose-response curves. Intensive Care Med 1994;20(5):319-327.
58. Bigatello LM, Hurford WE, Kacmarek RM, Roberts JD Jr, Zapol WM. Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. Anesthesiology 1994; 80(4):761-770.
59. Zapol WM, Rimar S, Gillis N, Marletta M, Bosken CH. Nitric oxide and the lung. Am J Respir Crit Care Med 1994;149(5):1375-1380.
60. Shaffer TH, Wolfson MR, Clark LC Jr. Liquid ventilation. Pediatr Pulmonol 1992;14(2):102-109.
61. Shaffer TH, Wolfson MR, Greenspan JS, Rubenstein SD, Stern RG. Perfluorochemical liquid as a respiratory medium. Artif Cells Blood Substit Immobil Biotechnol 1994;22(2):315-326.
62. Tutuncu AS, Akpir K, Mulder P, Erdmann W, Lachmann B. Intratracheal perfluorocarbon administration as an aid in the ventilatory management of respiratory distress syndrome. Anesthesiology 1993;79(5):1083-1093.
63. Pierson DJ, Capps JS, Hudson JD. Maximum ventilatory capabilities of four current-generation mechanical ventilators. Respir Care 1986;31(11):1054-1058.
64. Snider GL. Allocation of intensive care. The physician's role. Am J Respir Crit Care Med 1994;150(2):575-580.
65. Montgomery AB, Stager MA, Carrico J, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985;132(3):485-489.
66. Weiss SM, Hudson LD. Outcome from respiratory failure. Crit Care Clin 1994;10(1):197-215.
67. Gammon RB, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. Chest 1992;102(2): 568-572.
68. Marini JJ, Kelsen SG. Re-targeting ventilatory objectives in adult respiratory distress syndrome. New treatment prospects-persistent questions (editorial). Am Rev Respir Dis 1992;146(1):2-3.
69. Pierson DJ. Alveolar rupture during mechanical ventilation: role of PEEP, peak airway pressure, and distending volume. Respir Care 1988; 33(6):472-484.
70. Pierson DJ. Barotrauma and bronchopleural fistula. In: Tobin MJ, ed. Principles and practice of mechanical ventilation. New York, McGraw-Hill, 1994:813-836.
71. Kolobow T, Moretti MP, Fumagalli R, Moretti Mascheroni D, Prato P, Chen V, Joris M. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. Am Rev Respir Dis 1987;135(2):312-315.
72. Tsuno K, Prato P, Kolobow T. Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol 1990; 69(3):956-961.
73. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137(5):1159-1164.
74. Dreyfuss D, Saumon G. Ventilator-induced injury. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill, 1994:793-811.
75. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 1984;129(3):385-387.
76. Bellomo R, McLaughlin P, Tai E, Parkin G. Asthma requiring mechanical ventilation: a morbidity approach. Chest 1994;105(3): 891-896.
77. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990;16(6):372-377.
78. Hickling KG. Low volume ventilation with permissive hypercapnia in the adult respiratory distress syndrome. Clinical Intensive Care 1992;3:67-78.
79. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 1994;22(10):1568-1578.
80. Kacmarek RM, Hickling KG. Permissive hypercapnia. Respir Care 1993;38(4):373-387.
81. McIntyre RC Jr, Haenel JB, Moore FA, Read RR, Burch JM, Moore EE. Cardiopulmonary effects of permissive hypercapnia in the management of adult respiratory distress syndrome. J Trauma 1994;37(3): 433-438.
82. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? Am J Respir Crit Care Med 1994;150(6, Part 1):1722-1737.
83. Tuxen DV. Permissive hypercapnic ventilation. Am J Respir Crit Care Med 1994;150(3):870-874.
84. Bidani A, Tzouanakis AE, Cardenas VJ Jr, Zwischenberger JB. Permissive hypercapnia in acute respiratory failure. JAMA 1994;272(12): 957-962.

85. Steinberg KP, Hudson LD, et al. Causes of mortality in ARDS (abstract). Am Rev Respir Dis 1993;147(Suppl):347A.
86. Pingleton SK. Complications of acute respiratory failure. Am Rev Respir Dis 1988;137:1463-1493.
87. Strieter RM, Lynch JP. Complications in the ventilated patient. Clin Chest Med 1988;9(1):127-139.
88. Pierson DJ. Complications associated with mechanical ventilation. Crit Care Clinics 1990;6(3):711-724.
89. Consensus conference on the essentials of mechanical ventilation. Respir Care 1992;37(9):999-1130.
90. Marini JJ. Strategies to minimize breathing effort during mechanical ventilation. Crit Care Clin 1990;6(3):635-661.
91. Hansen-Flaschen J, Cowen J, Raps EC. Neuromuscular blockade in the intensive care unit. More than we bargained for. Am Rev Respir Dis 1993;147(1):234-236.
92. Craven DE, Kunches LM, Kilinsky V, Lichtenburg DA, Make BJ, McCabe WR. Risk factors for pneumonia in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1986;133(5):792-795.
93. Craven DE, Steger KA. Pathogenesis and prevention of nosocomial pneumonia in the mechanically ventilated patient. Respir Care 1989;34(2):85-97.
94. East TD. The ventilator of the 1990s. Respir Care 1990;35(3): 232-240.
95. Benson MS, Pierson DJ. Auto-PEEP during mechanical ventilation of adults. Respir Care 1988;33(7):557-565.
96. Marini JJ. Should PEEP be used in airflow obstruction? [Editorial] Am Rev Respir Dis 1989;140(1):1-3.
97. Pierson DJ. Measuring and monitoring lung volumes outside the pulmonary function laboratory. Respir Care 1990;35(7):660-668.
98. Lawless ST. Crying wolf: false alarms in a pediatric intensive care unit. Crit Care Med 1994;22(6):981-985.
99. Criner GJ, Isaac L. Psychological issues in the ventilator-dependent patient. Respir Care 1995;40(8):855-865.

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Mechanical Ventilation Innovations: The Manufacturer's Perspective

Douglas F DeVries

I. Background
II. The New-Product-Development Process
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Background

The top leaders of manufacturing companies have increasingly moved new products into a more central role in corporate strategies. The idea is to build businesses through the introduction of new products. As a result, recent years have seen company after company explicitly state the goal that, within 5 years, it will have 20%, 30%, 40%, or more of its revenue derived from new products. But, at the same time, the challenge of developing successful new products has become much tougher.[1] The process of bringing innovations in mechanical ventilation to the market is complex and involves manufacturers, clinicians, administrators, and regulatory agencies. Additionally, these new products must be brought to market quickly in order to be competitive and to generate an acceptable return on investment. As the complexity and cost of product development increase, the rate of product innovation decreases. To reverse this trend, manufacturers must work closely with clinicians, health-care administrators, and the regulatory community to streamline the process and, thus, ensure a continuing stream of effective new products.

The New-Product-Development Process

Developing new mechanical ventilation products is a lengthy process involving many phases. Most companies use some variation of the following chronologic process to bring new products to market:

1. Idea Generation. All products start with an idea. Ideas come from many sources, but, increasingly, the most successful product ideas originate with the customer.

2. Product-Idea-Evaluation Process. Most companies receive more product ideas than they have resources to develop. Consequently, the more successful companies develop an

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effective selection process that brings only the best ideas to market.

3. Product Development. Product development is an expensive process involving market research, engineering, documentation, regulatory approval, and product testing.

4. Manufacturing. New products most often entail significant costs in manufacturing startup, such as tooling and additional capital equipment required for production.

5. Sales and Service. The launching of a new product requires sales support in the form of literature, training, and advertising. Additionally, the product requires complete service support, such as manuals, spare parts inventory, and technical training.

At the end of each phase, the company typically reassesses the product development project to see whether it is consistent with the company vision and meets the established financial objectives. In this paper, I specifically address the first three phases of the process because these activities determine both the direction and rate of product innovation.

Product Ideas

In the past, many product ideas have been generated within the company. The descriptive term, technology-driven, conjures up images of a group of geniuses corralled in a think tank generating new product ideas. The customer has little input to the process (Henry Ford: "You can have any color as long as it is black.") In today's market-driven international economy, the customer typically has many competing product choices. Thus, successful companies must understand their customers' needs. It is my observation that customers are now the primary source of ideas. For mechanical ventilation, this group includes respiratory therapists, physicians, clinical researchers, and facility administrators. It is safe to say that more than 90% of the innovations in mechanical ventilation involving a different method of gas delivery originated either directly or indirectly from the clinical community. Conversely, the majority of ideas involving new technology that delivers ventilation more accurately or less expensively originate in product-development groups.

Traditionally, market research focused on users of large quantities of existing products. However, by definition these users may not be ahead of the trend. To stay ahead of the trend, many companies are turning to lead users or 'luminaries,' ie, customers and potential customers on the 'cutting edge' of the company's product line. By studying these individuals and their suggestions for new features, a manufacturer can develop leading-edge products.

Health-care reform and the pressure of cost containment have lead to another potential source of ideas. Both clinicians and administrators are looking for more cost-effective products. This suggests a broader definition of innovation, ie, an innovative product can be one that lowers medical costs while maintaining a level of excellence in patient care.

The Product-Idea-Evaluation Process

Most companies are deluged with product ideas and must develop an effective decision-making process to determine the best products to pursue. Although the process varies among companies, the following questions in some form must be satisfied:

Does the Product Fit the Corporate Vision?

All companies have a vision, either implicit or explicit. It is recognized that manufacturers become proficient at certain processes, often termed core competencies. These core competencies enable them to compete effectively in specific markets and should be aligned with the corporate vision. For example, a corporate vision may state, "ACME Manufacturing will be the leading supplier of disposable respiratory products in the world." To realize this vision, the company needs to develop core competencies in plastics manufacturing and international marketing. It is vital that new products be aligned with the company vision. Thus, if a clinician approached ACME Manufacturing with a concept for a new closed-loop high-technology ventilator, the idea would most likely be declined–and appropriately so.

Does the Product Fit the Manufacturer's Capabilities?

As previously discussed, manufacturers develop their capabilities to support the corporate vision. For example, a company that specializes in disposable products generally would have a smaller service organization than one focusing on respiratory monitoring equipment. Successful new products require effective support from all departments within a company.

What Are the Product Liability Risks/Costs?

Medical devices, by their nature, incur liability risks. Within the spectrum of medical devices, liability risks vary widely. For example, the failure of a simple incentive spirometer is less likely to cause patient injury than the failure of a ventilator. Risks drive product-development costs and ongoing manufacturing costs in many ways. Ventilators, for example, require in-depth hazard studies, failure modes and effects analyses, and reliability testing to ensure that hazards resulting from product failures can be eliminated or minimized. In addition, product liability insurance premiums charged to a manufacturer of life-support equipment are higher than the premiums for lower risk products. It is estimated that these companies spend 1-4% of total revenues on insurance premiums. The upper end of this range approaches the total research-and-development budget for some companies. These issues translate to a cost of doing business that must be carefully evaluated before a new product line is developed.

What Is the Current Market Size & Future Potential?

Prior to entering a new market, a company must thoroughly evaluate its size, growth potential, and competition. The ideal market is large and growing rapidly, with no single dominant competitor. This is specifically applicable to the respiratory device market, in which certain segments of the domestic ventilator market are flat or declining; whereas, specific regions of the international community are enjoying rapid growth. For example, the estimated total domestic adult ventilator market was only 6,000 units in 1993, with an average growth of 1.5% over the preceding 2 years.[2] Entry into a slow-growth or declining market can result in financial disaster even though the product is innovative.

What Is the Product-Development Cost?

Product development for mechanical ventilators can be costly. Modern ventilators usually consist of mechanical and electronic subsystems often controlled by software and requiring professionals from a broad range of engineering disciplines to develop. Engineering activities are only a part, and, in some cases, a minor part of the overall product-development costs. Increasingly, the cost of obtaining Food and Drug Administration (FDA) clearance in the U.S. and the cost of testing have become major components of the total product-development program. The remainder of this paper focuses on these last two activities.

In 1976, the FDA began regulating medical devices. This regulatory power was further strengthened by the passage of the Safe Medical Devices Act in 1990.[3] New products and modifications to existing products are subject to one of the following FDA processes:

- Pre-Market Application (PMA). This process is required when no pre-existing similar (predicate) device exists.
- Pre-Market Notification, 510(k). This is required to satisfy clinical efficacy when a predicate device exists. The process focuses on establishing substantial equivalence to the predicate device and ensuring that the development process meets FDA guidelines.
- Letter-to-File. The proposed modification does not affect safety or efficacy, in the FDA's opinion.

The result of invoking these processes has been a dramatic increase in the time and expense associated with regulatory approvals.

By definition, the most innovative new products are required to undergo the PMA process. The total average elapsed time for this process has steadily increased over the last decade, reaching 799 days in 1993. At the same time, the number of PMA submissions has decreased from a high of nearly 100 in 1988 to 40 in 1993. This decrease is a direct indicator of the level of product innovation.[4]

Similar trends are evident in the 510(k) clearance process. Figure 1 illustrates the average 510(k) clearance times for Bird Products Corporation over an 8-year period. Not only has the clearance time increased, but the amount of documentation required has dramatically expanded. Figure 2 illustrates the average page count for each submission during the same 8-year period. In my experience, this increased demand for documentation diverts time, talent, and money from the development process. As of this writing, high-frequency ventilation is the only currently marketed mechanical ventilation innovation that has been subjected to the PMA process. The high cost and delays associated with this approval are well known in the industry, providing a further dampening effect on innovations that may be subject to this process.

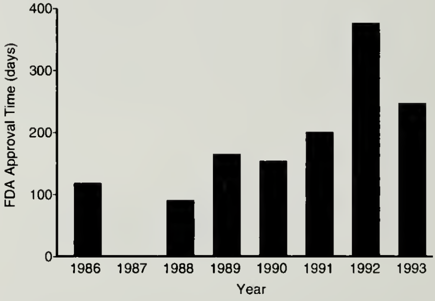

Fig. 1. Average 510(k) clearance time, 1986-1993. Bird Products Corporation

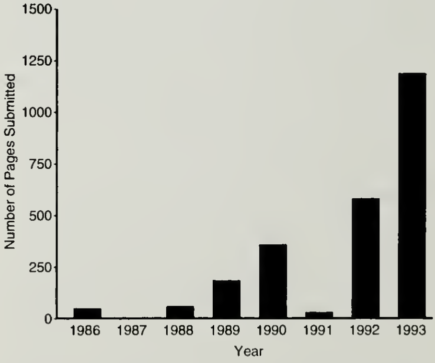

Fig. 2. Average 510(k) submission page count, 1986-1993. Bird Products Corporation

In general, the FDA approval process has had a strong negative impact on the rate of innovation in the field of medical devices. Companies are increasingly forced to test, manufacture, and market products in other countries prior to domestic introduction. The process has become the highest risk critical-path task in most product-development cycles.

What Testing Is Required To Establish Efficacy?

Product efficacy currently (1995) is established using one or more of the following methods:

- Bench testing
- User-preference testing
- Physiologic clinical trials
- Clinical outcome studies.

Figure 3 illustrates the relative cost of the various processes. As shown, bench testing is the least expensive process whereas clinical outcome testing is the most expensive. Actual costs vary from a few thousand dollars for simple bench testing on a minor product improvement to millions of dollars for a multisite study to establish clinical outcomes. In the past, the FDA 510(k) clearance process required bench and, optionally, user-preference testing to establish safety and efficacy; whereas, the PMA process required physiologic or clinical outcome studies. This practice has begun to change, with the FDA increasingly requesting clinical data for the 510(k) process. Ultimately, the company should conduct the level of testing necessary to validate the claims for the device.

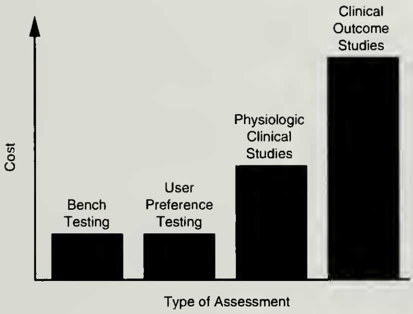

Fig. 3. Relative cost of the various assessment processes

What Is the Return on Investment?

The various development costs, development time, and revenue stream ultimately can be combined to estimate the return on investment. The actual financial model varies among manufacturers, but in the final analysis product opportunities that offer the greatest return over the shortest time are the most attractive. The following simplified examples illustrate this concept.

- Figure 4 is a simplistic graphic representation for a low-risk/low-cost device such as an oxygen blender. This device would typically require 510(k) clearance, bench testing, and possibly user-preference testing. As shown, the development cost could be $330,000, with a break-even time of 2.5 years.

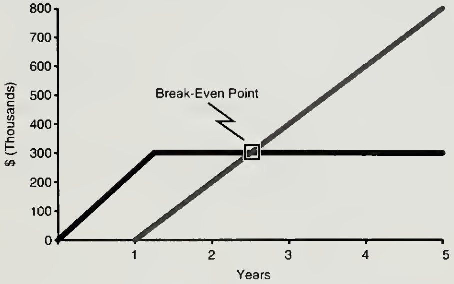

Fig. 4. Return on investment analysis for a low-risk/low-cost device, oxygen blender, indicating the break-even point between the development cost (▬) and cumulative revenues (▨).

- Figure 5 is a simplistic graphic representation of a high-risk/high-cost device such as a new closed-loop ventilator. This device typically requires all 4 levels of testing and a PMA. As shown, the development cost could be $15 million, with a break-even time of 7 years.

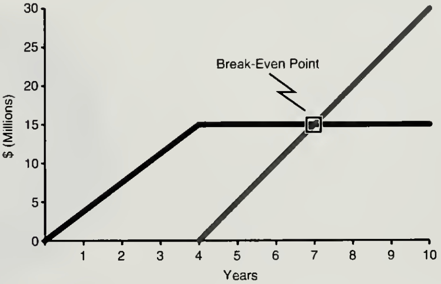

Fig. 5. Return on investment analysis for a high-risk/high-cost closed-loop ventilator, indicating the break-even point between the development cost (▬) and cumulative revenues (▨).

Few companies in the respiratory care industry can sustain this level of investment.

Discussion

Unlike the pharmaceutical industry, medical device manufacturers tend to be small, with limited resources for new-product development. Of the 18,250 medical device establishments registered with the FDA in 1993, 88% had fewer than 100 employees, and most of that 88% had fewer than 50 employees.[5]

Many of these small companies produce only a single product and have limited sales revenue, yet contribute significantly to product innovation. Others are startup companies that are dependent entirely on venture capital. Financing is limited, but desperately needed, for basic research-and-development work and to acquire the personnel and facilities to manufacture the new technology. This situation, coupled with the limited market potential for some innovations in mechanical ventilation make it difficult, if not impossible, for most manufacturers to fund lengthy and expensive clinical outcome studies.

Thus, it can be seen that the regulatory process and level of testing required can dramatically affect a company's decision to bring a new product to market.

Summary & Recommendations

- Manufacturers develop products that fit the corporate vision and maximize their return on investment.
- The expense and time required by the FDA regulatory approval process have a negative impact on product innovation. I propose the following approach:
    - Reduce the amount of documentation required for a PMA or 510(k).
    - Reduce approval times through cooperative interaction among manufacturers, clinicians, and the FDA throughout the product-development process.
    - Allow independent agencies to provide product approvals.
- Efficacy assessment guidelines should be a function of the level of risk and the claims made for the marketed device.

REFERENCES

1. Yovavich BG. New product cycle playing bigger role, Business Marketing, 1994;(Jan):33.
2. U.S. respiratory ventilator markets with supplemental customer perceptions and needs study. Biomedical Business International, Report #1810, 1993:4.4.
3. Public law 101-629. 104 Statute 4511. Safe medical devices act of 1990. November 28, 1990. Federal Register 1990;45(13):3751-3759.
4. U.S. Department of Health and Human Services, Center for Devices and Radiological Health, office of device evaluation annual report, fiscal year 1993.
5. Health Care Technology Institute, 1995 Reference guide for the health care technology industry, p. 5 (draft citing unpublished data from the Center for Devices and Radiological Health, FDA).

FACE TO FACE WITH CHANGE

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Introducing New Mechanical Ventilation Technology: The Hospital Perspective

Robert M Kacmarek PhD RRT

I. Introduction
II. Justifying Acquisition—A Theoretical Example
  A. Cost
    1. Capital Cost
    2. Ongoing Non-Capital Expense
    3. Repair
    4. Training
    5. Total Cost
  B. Benefit
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    2. Physiologic Response
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Introduction

In years past, respiratory care was a revenue source for hospitals, with departmental revenues exceeding costs by large margins. As a result, it was relatively easy to obtain new personnel and equipment. Large fleets of mechanical ventilators could be replaced, with no (or only minimal) supporting data from a cost-benefit perspective. In most hospitals that has changed dramatically as a result of managed care and capitation. Respiratory care is no longer viewed solely as a revenue center but more and more as a cost center.[1] Cost centers must justify the need to replace old technology with new technology or to add additional technology by projecting improved patient safety, decreased cost of providing the service, or improved patient outcome (eg, decreased length of stay, decreased number of ventilator days, or decreased morbidity).

Justifying Acquisition—A Theoretical Example

Much of the material presented here is based on my own experience and observations. In order to illustrate the cost-benefit issues associated with the introduction of new mechanical ventilation technology, I present a theoretical scenario—a community hospital with a 15-bed intensive care unit (ICU) and 15 mechanical ventilators. The ventilators are all 15 years old with limited capabilities when compared to current state-of-the-art mechanical ventilators. The respiratory care department and medical staff are seeking the financial support to replace these 15 ventilators.

Cost

A number of factors must be considered when the total cost of new mechanical ventilation technology is considered. Capital expense, although generally the largest individual component of the total cost of implementing any new technology, is only one of many factors to be considered. Ongoing non-capital expense, repair cost and service contracts, preventive maintenance, and cost of training ICU personnel are all factors that affect the total cost of introducing new technology.

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Capital Cost. In 1995, new critical-care mechanical ventilators with all of the options have list prices that range from $15,000 to about $35,000. This wide range in cost reflects available features and options that can be added. When one evaluates ventilators in this price range, a number of factors in addition to cost should be considered—the most important being the type of patient commonly ventilated. In an ICU that uses mechanical ventilators primarily for the 8 to 48 hours of postoperative recovery, the mechanical ventilators selected may differ markedly from those selected for a trauma or medical referral center with a large number of patients with acute respiratory distress syndrome. Available features should also be considered. If volume-limited assist/control with T-piece trials is the primary approach to ventilation and weaning in an institution, then mechanical ventilators with integrated pressure- and volume-targeted modes designed to allow computerized control of gas delivery (eg, volume-support or pressure-regulated volume-control) may not be considered necessary.

Continuing with our community hospital scenario, let us assume the cost of a new ventilator to be $25,000 (middle of range) for a total cost for 15 ventilators of $375,000. An additional cost frequently overlooked is shipping, which could amount to $250 for each ventilator or $3,750.

Ongoing Non-Capital Expense. I have observed that ongoing operational cost of new equipment is frequently overlooked when new technology is evaluated. For example, the purchase of ventilators that require a disposable flow transducer between the ventilator circuit Y and the endotracheal tube can add $18,300 in operating expense each year if the average daily mechanical ventilation census is 10 patients.

Disposable flow transducers @ $15.00 each
10 patients ventilated/day
Transducer changed every 3 days
(122 changes/year/patient)(10 patients/day)(15) = $18,300/year

If the transducer is reusable, the yearly cost may be less (about $9,000),

Permanent flow transducer @ $150.00 each
10 patients ventilated/day
Transducer replacement rate, 5/month
(5 changes/month)(12 months)(150) = $9,000/ year

but the cost of processing for reuse could easily be $5,000 or more yearly.

Estimated processing cost for permanent transducers $5,000/year
Total for permanent transducer use = $14,000/year

Because many accessories and components are disposable, we have found that small reusable items frequently are discarded or broken, explaining the replacement rate of 5 transducers/month. Further, a particular ventilator may require a specific humidifier or circuit or regular replacement of inspiratory and expiratory filters—requirements that add cost.

Our experience with unplanned-for costs of new technology—one, doubtless, shared by some of you—is the cost of disposable pulse oximetry probes. Because it was difficult to ensure proper fit and function with the original permanent (ie, nondisposable) probes, we began using disposable probes. In a large medical center like ours in which pulse oximeters are placed at each operating site (50 locations) and at each ICU bed (100 beds) and in which the turnover of ICU patients is rapid, the cost of disposable probes could easily reach $1 million/year. If one does not anticipate the cost of disposable probes because pulse oximeters come from the manufacturer with permanent probes then a large unplanned-for operational expense results.

Repair. I believe that most managers expect to save on repair costs or service contracts when new equipment is purchased. After all, one of the primary reasons for replacing equipment is frequent malfunction and associated high repair costs. However, with new microprocessor-ventilator systems, any repair out of warranty can mean replacement of a circuit board costing as much as $1,000. Careful negotiation for long-term maintenance and repair contracts at the time of purchase can greatly reduce overall costs during the initial years following purchase. However, even the best repair contracts can cost thousands of dollars each year for each ventilator after the warranty period. In addition, most new ventilators require specific preventive maintenance on a 3-month to 1-year basis. Both estimated repair and preventive maintenance cost for the new equipment and actual costs of the old equipment should be compared to ensure a complete description of total cost.

Preventive maintenance = $100/ventilator/0.5 year =
($200/ventilator/year)(15 ventilators) = $3,000/year

Service contract = $1,000/ventilator
(15 ventilators)($1,000) = $15,000/year

Total yearly cost = $18,000/year

Training. Another cost of introducing new technology frequently overlooked is training. Training bedside clinicians in the use of new technology is always necessary and, generally, is needed for both clinical trials of new equipment and the actual introduction of the purchased equipment. When new technology is introduced into the ICU, therapists, nurses, and physicians must be trained. In our specific example, let us assume that there are 10 staff therapists, 2 respiratory-care managers, and 1 biomedical repair technician who must master a newly introduced ventilator system. In addition, the 60 nurses who work in the ICU and 5 attending physicians and 5 residents assigned to the ICU must be oriented to the new ventilators.

Even before new technology is purchased, training is necessary for the clinical trial of any ventilator under consideration. In many hospitals, this may mean the trial of 3 or 4 ventilators for 1 to 2 weeks each. For each ventilator being clinically evaluated for possible purchase, lectures and laboratory sessions for a limited number of practitioners must be organized The time required to set up the trial ventilator, monitor its function, and discontinue its use also represents added cost. Because it is not feasible to train all staff to operate each trial ventilator, these trials usually mean set-up of the ventilator in the morning and return to the current ventilator at the end of the day shift. Total cost of ventilator trials may amount to $2,500-$3,000 and the training cost to introduce a newly purchased ventilator can, in this example, approach $7,000.

Training Hours & Cost for Clinical Trials *(2-week evaluation of 4 different ventilators for 8 days each)*

Therapist's Time & Cost

Therapist training at 2-hour lecture/lab for 5 therapists for each ventilator
(2 h/therapist)(5 therapists)(4 ventilators) = 40 hours

2-hour set-up and discontinue/ventilator/day in use
(2 hours)(4 ventilators)(8 days) = 64 hours.

Total 104 hours @ $17.50 = $1,820

Physician's Time & Cost
(1 h)(5 physicians)(4 ventilators) = 20 hours @ $50.00 = $1,000

Training Hours & Cost For Introduction of New Ventilator

Therapist's Time & Cost

Therapist instruction & competency evaluation
(3 hours)(13 therapists) = 39 hours
Therapists' direct supervision of nurses during first 20 patients
(4 hours/patient) = 80 hours
Nurses' instruction by therapist
(1 hour)(12 groups of 5 nurses) = 12 hours
Physicians' instruction by therapists = 5 hours

Total therapist-time cost for 136 hours at $17.50 = $2,380

Nursing Time & Cost
(1 hour)(60 nurses) @ $20.00 = $1,200

Physician Time & Cost
(1 hour)(5 physicians) @ $50.00 = $250

Time-Cost for Clinical Trials & Introduction = $6,650

Total Cost. The total cost of introducing new technology can be large ($421,700). In our example, the majority of the cost ($375,000) is for the actual purchase; however, training and ongoing non-capital costs can have a large effect on operating budgets.

Total First Year Cost of 15 New Ventilators

15 ventilators at $25,000 each	$375,000
Shipping cost at $250/ventilator	3,750
Ongoing cost for disposable accessories	18,300
Repair & Preventive maintenance	18,000
Training	6,650
Total	$421,700

Benefit

Considering the high cost of introducing new mechanical ventilator technology, benefit from the introduction should offset this high cost—if not immediately, then over time. However, demonstrating benefit is more difficult than establishing overall cost. As discussed elsewhere in this issue of the Journal,[2] benefit can be defined at many levels: increased revenue, improved safety, enhanced physiologic response and improved outcome. Revenue arguments in the past have been a primary method of establishing the benefit of new technology. In the era of fee-for-service, the cost was simply passed on to the patient. Today, reimbursement is generally not affected by the introduction of new technology unless other benefits can be established that affect outcome, thereby reducing the total cost of medical care.

Safety. Increased safety is an easily measurable effect of new technology. Justification for the replacement of older ventilators can sometimes be accomplished by demonstrating the increased safety that results from the improved monitoring capabilities of newer units.

Inadvertent ventilator disconnect or malfunction with no consequent sounding of alarms is easily demonstrated with first- or second-generation ventilators. It can be argued that iatrogenic risk is reduced with new technology. The introduction of pulse oximetry as a standard of care in the operating room and postanesthesia recovery room was based on the incidence of unrecognized life-threatening episodes of arterial desaturation prior to the introduction of this technology.[3] Cooper et al[4] documented the effect of pulse oximetry on the frequency of cardiovascular events in postanesthesia recovery. The incidence of hypertension and hypovolemia greatly decreased with the use of pulse oximetry. Pulse oximeters are now at each operating location and at most recovery beds because of the improved patient safety demonstrated after their addition to standard monitoring systems.

Physiologic Response. Improved physiologic response is frequently the primary benefit advertised with the introduction of new ventilator technology. Numerous articles now illustrate the fact that patient effort during spontaneous breathing is markedly reduced by the use of pressure support[5-7] or the change from pressure- to flow-triggering.[8-10] However, it is more difficult to prove that one mode of ventilation is more capable of producing a better physiologic response than another. A good example is pressure-control ventilation. Although arguments can be made for the ease of maintaining targeted system pressure or peak alveolar pressure with pressure control (as contrasted with volume control), no definitive data demonstrating improved physiologic response are available. Early uncontrolled trials indicated improved physiologic response with pressure control;[11-14] however, subsequent controlled trials have shown that the use of pressure or volume-targeted ventilation at normal inspiratory-to-expiratory time ratios or extended inspiratory time is equivocal in relationship to hemodynamics, gas exchange, and pulmonary compliance.[15-17]

Many of the innovative changes in ventilator design do result in improved patient-ventilator synchrony. Volume-support and pressure-regulated volume control available on the Servo 300 ventilator have improved the function of pressure support and pressure control.[18] These modes ensure control over both tidal volume and peak alveolar pressure; they both respond rapidly to changes in patient demand or pathophysiology. Flow or pressure augmentation on the Bear 1000 improves patient-ventilator synchrony by decreasing work of breathing.[19] However, it could be argued that more careful attention to changes in a patient's ventilatory pattern and more frequent ventilator adjustments by practitioners would result in the same response. Although improvement in physiologic response is important, in today's health-care financial environment improved outcome is the key to documenting the benefit of innovative technology.

Outcome. Measurements with the potential of demonstrating improved patient outcome (ie, factors that affect morbidity and cost of patient care) include

- Survival
- Number of days of mechanical ventilation
- Number of days in the ICU
- Number of days hospitalized
- Frequency of barotrauma
- Nosocomial infection rate.

However, it is difficult to identify studies that have demonstrated improved patient outcome as a consequence of the use of innovative mechanical ventilator technology. One good example is the recent study by Kramer et al[20] on the use of the Respironics BiPAP ventilator to manage acute respiratory failure. They showed that the use of noninvasive ventilatory support decreased the frequency of endotracheal intubation compared to conventional management of an acute COPD exacerbation. However, it can be argued that the improved outcome was not related to the ventilator per se but to the use of noninvasive ventilation, which has been demonstrated by numerous authors,[21-24] using many different ventilators, to improve physiologic response.

In November 1994, in an article by Brochard et al,[25] pressure-support weaning was reported to result in a shorter period of mechanical ventilation than did synchronized intermittent mandatory ventilation (SIMV) or T-piece weaning. However, in January 1995, Esteban et al[26] in a similar randomized trial showed that T-piece weaning (as compared to pressure support or SIMV) resulted in the shortest ventilator course. Based on these data, one might argue that it is not the technology itself that affected outcome, but the way the clinicians used existing technology that affected the length of mechanical ventilation. The clinician's more appropriate use of existing technology[27-30] appears to be the reason a number of centers have shown improved outcome with the use of permissive hypercapnia and a low peak alveolar pressure-targeting approach to ventilation. In theory, this improvement in outcome could be achieved with any available ventilator.

Summary

The introduction of innovative mechanical ventilation technology requires a careful assessment of the cost-benefit relationship of the new technology. Justification for purchase can be sometimes be made on the basis of improved patient safety and physiologic response. Improved patient outcome is much more difficult to demonstrate. It is clear in today's health-care environment that outcome-based research is needed before new technology is introduced to the marketplace, if that new technology is to become part of the average community-hospital complement of mechanical ventilators.

REFERENCES

1. Le Bouef LL. One respiratory care department's contribution to the 'bottom line.' Respir Care 1994;39(7):740-745.
2. Consensus Conference III: assessing innovations in mechanical ventilatory support. Respir Care 1995;40(9):925-993.
3. Coté CJ, Goldstein EA, Coté MA, Hoaglin DC, Ryan JF. A single-blind study of pulse oximetry in children. Anesthesiology 1988;68(2):184-188.
4. Cooper JB, Cullen DJ, Nemeskal R, Hoaglin DC, Gevirtz CC, Csete M, Veneble C. Effects of information feedback and pulse oximetry on the incidence of anesthesia complication. Anesthesiology 1987;67(5):686-694.
5. Ershowsky P, Krieger B. Changes in breathing pattern during pressure support ventilation. Respir Care 1987;32:1011-6.
6. Hurst JM, Branson RD, Davis Jr K, Barrette RR. Cardiopulmonary effects of pressure support ventilation. Arch Surg 1989;124(9):1067-1070.
7. Brochard L, Pluskwa F, Lemaire F. Improved efficacy of spontaneous breathing with inspiratory pressure support. Am Rev Respir Dis 1987;136(2):411-415.
8. Sassoon CS, Lodia R, Rheeman CH, Kuei JH, Light RW, Mahutte

CK. Inspiratory muscle work of breathing during flow-by, demand-flow, and continuous-flow systems in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;145(5):1219-22.

9. Sassoon CS, Giron AE, Ely E, Light RW. Inspiratory work of breathing on flow-by and demand-flow continuous positive airway pressure. Crit Care Med 1989;17(11):1108-1114.
10. Banner MJ, Blanch PB, Kirby RR. Imposed work of breathing and methods of triggering a demand-flow continuous positive airway pressure system. Crit Care Med 1993;21(2):183-190.
11. Tharratt RS, Allen RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe adult respiratory failure. Chest 1988;94(4):755-762.
12. Lain DC, DiBenedetto R, Morris SL, Nguyen AV, Saulters R, Causey D. Pressure control inverse ratio ventilation as a method to reduce peak inspiratory pressure and provide adequate ventilation and oxygenation. Chest 1989;95(5):1081-1088.
13. Abraham E, Yoshihara G. Cardiorespiratory effects of pressure controlled inverse ratio ventilation in severe respiratory failure. Chest 1989;96(6):1356-1359.
14. Abraham E, Yoshihara G. Cardiorespiratory effects of pressure controlled ventilation in severe respiratory failure. Chest 1990;98(6):1445-1449.
15. Mercat A, Graini L, Teboul JL, Lenique F, Richard C. Cardiorespiratory effects of pressure controlled ventilation with and without inverse ratio in the adult respiratory distress syndrome. Chest 1993;104(3):871-875.
16. Lessard MR, Guerot E, Lorino H, Lemaire F, Brochard L. Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress. Anesthesiology 1994;80(5):983-991.
17. Mang H, Kacmarek RM, Ritz R, Wilson RS, Kimball WP. Cardiorespiratory effects of volume- and pressure-controlled ventilation at various I:E ratios in an acute lung injury model. Am J Respir Crit Care Med 1995;151(3, Part 1):731-736.
18. Kacmarek RM, Hess D. Basic Principles of Ventilator Machinery. In Tobin MS (ed), Principles and Practice of Mechanical Ventilation. McGraw-Hill Pub. 1994 pp. 65-110.
19. Amato MBP, Barbas CS, Bonassa J, Saldiva PH, Zin WA, deCarvalho CR. Volume-assured pressure support ventilation (VAPSV). A new approach for reducing muscle workload during acute respiratory failure. Chest 1992;102(4):1225-1234.
20. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995;151(6):1799-1806.
21. Brochard L, Isabey D, Piquet J, Amaro P, Mancebo J, Messadi AA, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 1990;323(22):1523-1530.
22. Meduri GU, Conoscenti C, Manashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest 1989;95(4):865-870.
23. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, et al. Randomized controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993;341(8860):1555-1557.
24. Wysocki M, Tric L, Wolff MA, Gertner J, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. Chest 1993;103(3):907-913.
25. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994;150(4):896-903.
26. Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdi I, et al. A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med 1995;332(6):345-350.
27. Sheridan RL, Kacmarek RM, McEttrick MM, Uber JM, Doody DP, Ryan DP, Shnitzer JJ, Tompkins RG. Permissive hypercapnia as a ventilatory strategy in burned children: Effect on barotrauma, pneumonia and mortality. J Trauma (in press).
28. Kacmarek RM, Hickling KG. Permissive hypercapnia. Respir Care 1993;38(4):373-387.
29. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume, pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990;16(6):372-377.
30. Darioli A, Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 1984;129(3):385-387.

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FDA: The Regulatory Process

Arthur S Slutsky MD

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Introduction

In many countries, necessary steps before bringing any product to market involves participation in and compliance with mandates of the regulatory process. The specifics of this process vary substantially, with different mandates, requirements, and procedures in each country. In some countries, prior to bringing a product to market, it is sufficient to prove that the product is safe; in the United States, the law states that new medical devices must be proved safe *and* efficacious before they can receive regulatory approval.[1] In this paper, I focus on the regulatory process in the United States, a process that is administered by the Food and Drug Administration (FDA). I highlight some historical aspects of the FDA, present an overview of how the FDA classifies devices, summarize briefly the pathways to market for a new medical device, and, finally, present a few personal suggestions to improve the process.

Historical Perspective

The concept of society's regulating products that are to be consumed or used is not a new one.[2] The ancient Egyptians and Hebrews had strict laws governing which foods could be eaten and even how to appropriately prepare those foods. The Greeks and Romans had important laws prohibiting the dilution of wine with water. The Magna Carta signed in 1215 A.D. had a provision that could be considered regulatory in that it sanctioned only one system of weights and measures.

The modern laws regulating food and drug products grew out of the industrial revolution and the growing trend to urbanization. When individuals raised and prepared their own foods, such laws may not have been necessary. However, problems developed over time. In the early 19th century, the United States had no standards and was considered the world's dumping ground for various foods of dubious quality. In the late 19th century, a number of patent medicines promised cures for cancer, diabetes, and lost manhood, and a number of medications contained heroin, opium, and/or cocaine—many of which were

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used for infants.[2] Of particular interest to the topic addressed during the Consensus Conference is a patent granted to Alfred F Jones in 1864 for what would now be considered an iron-lung-type ventilator. In the patent, Jones stated that the device "cured paralysis, neuralgia, seminal weakness, asthma, bronchitis and dyspepsia. Also deafness ... and when judiciously applied, many other diseases may be cured."

The first major legislation addressing regulation of these items was the Pure Food and Drugs Act of 1906, also called the Wiley Act. This Act resulted from growing public concern about these products, as well as evolutionary changes in the practice of medicine that had developed a better understanding of the pathophysiology of disease as well as more efficacious treatments. In 1927, the Bureau of Chemistry was reorganized to the Food, Drug, and Insecticide Administration, and, in 1931 the name was changed to the Food and Drug Administration.

The major piece of legislation that forms the basis of current regulations was entitled the "Food, Drug, and Cosmetic Act," which was passed in 1938. The impetus for this legislation was a tragic incident in 1937 in which diethylene glycol was used as solvent for sulfanilamide and 107 people, mainly children, died. This legislation provided for factory inspections, scientific proof by manufacturers, prosecution for false claims, and adequate labeling of food and drugs.[2]

The 1976 Amendment of the Food, Drug, & Cosmetic Act

Definitions

The 1976 Amendment is the major piece of legislation that provides the framework for current regulations. It defined the term device, provided a regulatory system based on the degree of risk, and mandated pre-market procedures similar to those required for drugs, with approval based on clinical experience. The Amendment also established Advisory Panels and some procedures for post-market surveillance. A key section of this amendment is a 'grandfather' clause, Section 510(k) of the Act, that is described later.

The definition of a medical device is broad and includes any product, used for the diagnosis, cure, medication, treatment, or prevention of a disease or condition, that does not achieve its intended use through chemical action and is not metabolized. This definition is all encompassing and covers approximately 50-100,000 separate products, 1,700 different types of products, and 7,000 manufacturers.

Classification Systems

The 1976 Amendment classified medical devices in two ways. The first is based on the degree of regulation necessary to ensure the safety and effectiveness of a device, with a strong relationship to the degree of risk engendered by the product. Class-I devices are relatively simple devices that present little risk to patients. For these, as well as for Class-II and Class-III devices, manufacturers must comply with a number of regulations including 'pre-market' notification, record-keeping, labeling, reporting, and Good Manufacturing Procedure (GMP) practices. Class-II devices are devices in which safety and efficacy could be assured with federally defined performance standards. Class-III devices are those that require greater controls and greater evidence of safety and efficacy. To bring Class-III devices to market, the pre-market application (PMA) process must be used (see below).

The second way that the 1976 Amendment classified devices was according to the following categories:[3]

- Transitional devices, which are devices that had been regulated as drugs prior to 1976
- Implanted devices
- Custom devices
- Investigational devices (IND)
- Pre-Amendment devices that were on the market before May 28, 1976 (the date of Amendment passage)
- Substantially equivalent devices
- Post-Amendment devices (new devices).

All pre-Amendment Class-III devices and their substantially equivalent counterparts (see below) were allowed to remain on the market until the FDA took specific regulatory action. Post-Amendment devices that were not deemed substantial equivalents were automatically placed into Class III.

The 1990 Safe Medical Devices Act

In 1990, another major amendment entitled the Safe Medical Devices Act (SMDA) was passed.[1] The rationale for this amendment was perceived problems with the 1976 law. Proponents of the amended law believed that the process for determining substantial equivalence [often called the 510(k) process] represented a loophole through which untested products were allowed to reach the market. In addition, proponents believed that the 1976 law did not give sufficient regulatory authority to the FDA to deal with issues related to post-market surveillance. It is interesting that although this set of amendments was debated for many years during the 1980s, the political will to pass these amendments was provided by the revelation in the late 1980s that bribery and submission of false data had been used in connection with certain generic drug approvals.[4]

The 1990 SMDA[1] provides a number of changes to the PMA process, post-market surveillance, and penalties. It changes the 510(k) process from a notification process to an approval process, with requirement for clinical data when necessary and allowance for the use of special controls, such as voluntary standards. In addition, the FDA can use data from previous submissions to process new submissions after four new products in a given category have been approved. With regard to post-market surveillance, the law makes high-risk products subject to FDA-regulated surveillance and mandates that health-care institutions be required to report incidents if a device is thought to contribute to a patient's death. The FDA is also given greater authority to suspend approved applications, to recall devices, and to impose fines.

Pathways to Market

Investigational Device Exemption (IDE)

In order to collect the data required to show safety and effectiveness of a new device or a new indication for a marketed device, it may be necessary to perform studies on humans. The IDE provides the mechanism by which investigators and manufacturers can legally test devices on humans. These regulations and the requirements are described in an FDA document.[5] The critical concept is that devices posing a significant risk to patients require approval by both the FDA and the Investigational Review Board (IRB) of the hospital involved. Devices that are considered to pose an insignificant risk (as ascertained by the IRB) may be studied with the approval of the local IRB; an IDE is considered 'approved' if this and other requirements are met. No IDE application to the FDA is required.

Substantial Equivalence: The 510(k) Process

The rationale underlying this section of the 1976 Amendment is to ensure fair treatment of new devices, such that they do not have to overcome greater regulatory hurdles compared to similar devices that were on the market prior to May 28, 1976 (the date the law was passed). This is the simplest and quickest route to market, with a substantially lower approval time than the PMA. Many more 510(k) applications are submitted than are PMA applications. Since 1976, for devices related to mechanical ventilation, only 5 applications for high frequency ventilators have received PMA approval, whereas numerous 510(k) applications have been approved.

No generally applicable specific guidelines definitively ascertain that a device is substantially equivalent. As guidance, a Congressional Committee has stated that the determination of substantial equivalence is "not intended to be so narrow as to refer only to devices that are identical to marketed devices, nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products."[6] A device can be considered substantially equivalent if it is found to be similar to two types of devices, called predicate devices: (1) a device sold before May 28, 1976 for which PMAs have not been called, and (2) a post-Amendment device that is marketed and found to be substantially equivalent to the pre-Amendment device that has been reclassified to Class I or II. An overview of the approach taken by the FDA to determine whether a device is substantially equivalent is given in Figure 1. The critical issues are whether the device has the same intended purpose as a predicate device and whether it has the same technologic characteristics. If the new device makes use of new technology, the critical question is whether this new technology can affect the safety and effectiveness of the device. As long as the questions of safety and efficacy posed by the new technology are similar to those posed by the old technology and as long as there are scientific methods for evaluating the question, the device can be deemed substantially equivalent.

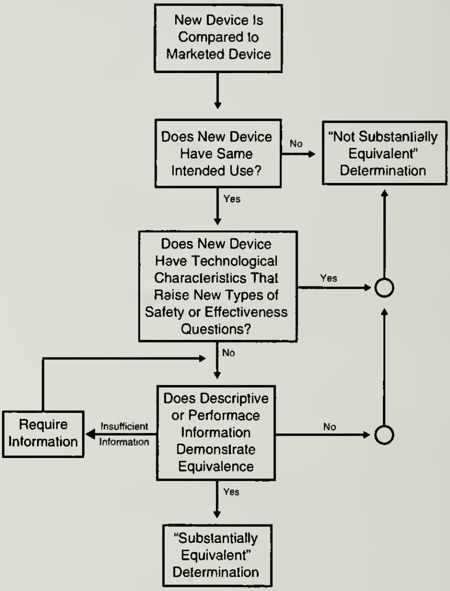
New Device Is Compared to Marketed Device
Does New Device Have Same Intended Use?
No
"Not Substantially Equivalent" Determination
Yes
Does New Device Have Technological Characteristics That Raise New Types of Safety or Effectiveness Questions?
Yes
No
Require Information
Insufficient Information
Does Descriptive or Performace Information Demonstrate Equivalence
No
Yes
"Substantially Equivalent" Determination

Fig. 1. Flow chart indicating decision-making process for determining substantial equivalence of a new device, as compared to a device already marketed. (Reprinted from Reference 6)

Pre-Market Application

An approved PMA is an individual license permitting only the applicant to market the specific device; the application must contain detailed information providing a description of manufacturing processes, clinical data from the IDE, a summary of the safety and effectiveness of the device, other information available to the manufacturer (eg, relevant literature), and proposed labeling for the product.[7] Under the rubric of a PMA, the critical issue for the manufacturer is to prove to the FDA that the product is *safe* and *effective* for the stated use. In terms of safety, the manufacturer must provide "...reasonable assurance that probable benefits to health (under conditions of use) outweigh probable risk." It is important to note that the risk-benefit must be acceptable, but it is not required that the product never cause injury or always be effective. In terms of effectiveness, there must be "... reasonable assurance that ... use of the device ... will provide clinically significant results."[7]

The statutory standard for devices is different from that for new drugs. For drug approval, adequate, well-controlled investigation by qualified experts are required; whereas, for devices, "valid scientific evidence" is also acceptable. Valid scientific information includes well-controlled studies, scientifically controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device. Isolated case reports, unsubstantiated opinion, and reports lacking sufficient details are not considered valid scientific information to prove safety and effectiveness.

When a PMA is received by the FDA, a copy goes to the appropriate division for filing review, to the operations staff with respect to inspection of manufacturing sites, and to statistical review. A decision to file or not to file should be made within 45 days. If the FDA agrees that the application has sufficient information to be filed, the statute states that the decision regarding approval must be made within 180 days of filing.[8] My impression is that in past years, the average time for decision has been substantially longer than 180 days. If the FDA decides that the PMA should not be filed, it must specify the reasons and advise the applicant what steps are required to make the application suitable for filing. After the application has been filed, it is then evaluated by the FDA staff and the Advisory Panel, which is composed of 7 voting members who are knowledgeable in the field, a consumer representative, an industry representative, and consultants as required. The final decision, however, is made by the FDA staff.

The regulations described above and the implementation of these regulations have had 'mixed reviews' with respect to their effectiveness. The U.S. standards for approval of drugs and devices are among the most stringent in the world; and, thus, products that are approved for marketing in the U.S. are usually accepted in most other countries.[9] However, there are those who believe that this high standard is also associated with a process that is slow and cumbersome,[10] making it time consuming and expensive. On the other hand, there are those who believe that the current system should have even tougher controls especially in relation to the use of outdated bases (pre-1976 devices) and that the post-market-surveillance system is ineffective.[11,12] Many but not all of these issues have been addressed by the 1990 Law.[13]

The impact of these issues on the consumer is of interest. The public is taking a greater interest in the regulatory process, with greater public scrutiny of the FDA. This is particularly evident related to new pharmaceuticals for the treatment of AIDS. Patients are eager to make the risk-benefit assessments that are under the jurisdiction of the FDA.[14] Independent panels that have addressed these issues have concluded that the FDA lacks focus, is hampered by its bureaucracy, and requires better management;[15] whereas, others have called for changes in the organizational structure of the FDA.[16]

Suggestions

Given this background, I propose:

For the FDA:

- Encourage even more interaction between the FDA and industry in the development of appropriate applications, especially early in the process.
- Establish priorities—put resources where they are really needed and simplify the process for "simple items." It is important to prioritize according to importance.
- Reduce documentation for 510(k) and PMA as much as possible; make the PMA process more like the 510(k) process.
- Remember that approval of safe new products can be as important to public health as is the prevention of marketing harmful or ineffective ones.

For the Manufacturer:

- Plan ahead for application—consult with FDA personnel very early in the submission process (even in the pre-IDE period).
- Petition for reclassification where indicated.
- Work with voluntary organizations such as the American Society for Testing and Materials (ASTM) and the Association for Advancement of Medical Instrumentation (AAMI) to develop standards or guidelines where appropriate.
- Find out what general guidelines are available for the application (eg, for software, electrical issues, and formal submissions).
- Decide what the specific indications for the device are, and design appropriate studies to address these indications. The crucial issue is to have appropriate, statistically meaningful conclusions. Common mistakes made in the PMA process are lack of justification of sample size, failure to follow protocol, failure to state hypothesis or incorrect statement of hypothesis, failure to test hypothesis correctly, unjustified pooling of data, failure to evaluate potential bias, failure to define end points clearly, and failure to utilize blinded end points.[7]
- Finally, present a coherent and well-written PMA.

For Congress:

- As stated by the Edwards Committee, the FDA is "overextended, underfunded, and shackled by bureaucratic constraints."[17] In many ways, the regulations governing devices are reasonable, but the FDA should have resources to apply these regulations in a timely manner.

- Increase flexibility in the regulations by simplifying the PMA process and consider approaches to simplifying the Conflict of Interest Guidelines, which are incredibly labor intensive and exclusionary.
- Make the FDA more independent[15] and consider independent bodies to review PMAs.
- Enter and/or continue negotiations with other countries to rationalize regulatory requirements internationally.

Conclusions

A well-developed regulatory process is critical to ensure the safety and efficacy of new medical devices; however, this same regulatory process makes it more difficult and expensive for new products to be brought to market. Although current legislation was designed to ensure efficient processing of submitted applications, the FDA is under pressures that make it inherently conservative. If significant morbidity or any mortality can be blamed on a device regulated by the FDA, the public and the Congress can put tremendous pressure on the FDA to justify the approval process. Thus, the natural tendency is for the FDA to ensure that absolutely no devices receive approval that are not safe. Of course, on one level, this is exactly their role. However, this approach can lead to failure to approve devices even though they may be of tremendous benefit to some patients. The families of patients who die because they have not received the benefits of a device that has not as yet been approved do not even know that there might have been an alternative for them, and, thus, are not a vocal constituency complaining to Congress or the FDA.

It appears to me that the legislation currently available to regulate this difficult balancing act appears reasonable, but, it also appears that sufficient resources have not been allocated to the FDA to ensure the timeliness of reviews as proposed in the legislation. Another major issue that greatly increases costs and delays innovative devices from reaching market is a lack of uniformity among the countries in their regulatory processes. Valid reasons may exist for such discrepancies, but we can only hope that, as trade among nations becomes more open, this process will become more uniform.

REFERENCES

1. Public law 101-629. 104 Statute 4511. Safe medical devices act of 1990. November 28, 1990. Federal Register 1990;45(13):3751-3759.
2. Ziporyn T. The Food and Drug Administration: how those regulations came to be. JAMA. 1985;254(15):2037-2039, 2043-2046.
3. Kessler DA, Pape SM, Sundwall DN. The federal regulation of medical devices. N Engl J Med 1987;317(6):357-366.
4. Samuel FEJ. Safe medical devices Act of 1990. Health Aff 1991; 10(1):192-195.
5. Investigational device exemptions manual. Rockville, Maryland: U.S. Department of Health and Human Services, 1992.
6. Pre-market notification 510(k): Regulatory requirements for medical devices. Rockville, Maryland: U.S. Department of Health and Human Services, 1992.
7. Pre-market application (PMA) manual. Rockville, Maryland: U.S. Department of Health and Human Services, 1993.
8. CFR, Chapter 21. Part 814.
9. Appler WD, McMann GL. FDA in the 1990s. American Pharmacy. 1990;NS30(5):27-32.
10. Pillar P. Nursing & Technology: The safety of medical devices and the role of the FDA. Nursing Economics. 1991;9(4):284-286.
11. Bowsher C. Statement to the subcommittee on health and the environment, committee on energy and commerce, house of representatives (GAO/T-PEMD-90-2). Washington DC: General Accounting Office, 1989.
12. Shedlin R. The FDA: Is it protecting the public with one hand tied behind its back? Law, Medicine & Health Care. 1992;20(3):253-257.
13. Kessler DA. FDA's revitalization of medical device review and regulation. Biomed Instrum Technol. 1994;28(3):220-226.
14. Samuel FE Jr. On FDA's future. American Pharmacy. 1991;NS31, No.8:35-37.
15. Martin S. Two panels say FDA needs better management, should be independent. American Pharmacy. 1991;NS31, No.8:34-36.
16. Watson JT. Food and drug administration guidance sections. A new paradigm for medical devices. ASAIO J. 1994;40(2):138-144.
17. Iglehart JK. The Food and Drug Administration and its problems. N Engl J Med 1991;325(3):217-220.

Case Studies on Mechanical Ventilator Innovations: Perspectives of Two Clinicians

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Preface

In 1994 in preparation for the Consensus Conference, "Assessing Innovations for Mechanical Ventilatory Support," we spent several months in conversation and correspondence with clinicians, manufacturers and product developers, and others. The discussions centered on the regulation of medical devices and the processes of assessing and gaining approval for new products and modifications of existing products. Of those approached, many shared their experiences and perceptions with us, but only with the stipulation that the source of the information not be revealed. That stipulation left us in a quandary. We are clinician-researchers—not fiction writers or tabloid contributors—and we were reared to avoid anecdote and opinion and to insist on responsible documentation and balanced reporting of published data. However, we had accepted the challenge of the Conference Chairmen to provide "...case studies in recent innovations ... [the flaws] in the process of establishing efficacy ... [and] how safety and efficacy were established for flow-triggers, pressure support, inverse ratio ventilation, and high-frequency ventilation." We believed it important to provide first Conference participants and now readers with an account of attempts to have products assessed and approved. This paper encompasses that account.

Introduction

As the result of the Medical Device Amendment passed by Congress on May 28, 1976,[1] the FDA was given the authority to regulate medical devices. All medical devices are placed into one of three categories: Class I (General Con-

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trols), Class II (Performance Standards), Class III (Pre-Market Application, or PMA). Devices placed into Class I are subject to the least strenuous control, whereas Class-III devices are the most heavily regulated. Class-I devices are exempt from Class-II and Class-III regulations. Obtaining an FDA exemption can be as difficult as completing the 510(k) application process, and we have observed that many manufacturers of medical devices avoid Class-I designation. Table 1 provides examples of medical devices in each of the three classes.

Table 1. Medical Device Classification with Examples of Each

Class-I Devices	Esophageal stethoscopes Blow bottles Nose clips Nasal oxygen cannulas Breathing mouthpieces Tracheobronchial suction catheters
Class-II Devices	Oxygen, nitrous oxide, and halothane gas analyzers Diagnostic spirometers Autotransfusion apparatus Anesthesia breathing circuits Ventilators for continuous support All pulmonary function meters
Class-III Devices	Indwelling oxyhemoglobin concentration analyzers Indwelling carbon dioxide analyzers Lung water monitors Extracorporeal membrane oxygenators High-frequency ventilators (rates > 150/min)

Continuous mechanical ventilators are Class-II devices. The original intention of the Medical Device Amendment was to write performance standards for Class-II devices. However, mandatory performance standards for ventilators have yet to be written. We have observed that manufacturers typically gain approval to market Class-II devices through the 510(k) process, which requires evidence that the device (eg, ventilator) be shown to be substantially equivalent to a pre-Medical Device Amendment device (Fig. 1). This requires that the manufacturer demonstrate, through testing and prior art (ie, previously submitted technical drawings, laboratory data, and specifications), that the new device is substantially equivalent to a device that had been approved before 1976. FDA scrutiny of 510(k) applications is becoming increasingly rigorous, requiring large volumes of laboratory validation testing and Customer Preference Testing before the device is approved.

The introduction of microprocessor technology has further complicated this process. Current FDA regulations[1,2] require line-by-line testing of software to help reduce 'bugs' to a minimum. The software safety requirements significantly increase the necessary documentation for the 510(k) process and, coupled with the lengthy testing, cause costs and time-to-market to skyrocket. In the end, the consumer must pay this additional cost.

Class-III devices are those that are life-sustaining or life-supporting and for which substantial equivalence cannot be determined. An example of a Class-III device is a high-frequency ventilator. To market a Class-III device, manufacturers are required to submit a PMA. The FDA requires safety and efficacy studies before it will approve Class-III devices. This involves FDA approval of an Investigation Device Exemption (IDE), so that clinical trials can be conducted before FDA approval to market the device is granted. Corporate records suggest that it is very expensive to market Class-III devices and typically requires years of development and clinical trials.

Customer Preference Testing

Clinical trials of safety and efficacy are not required for Class-II devices. However, information related to the clinical use of a ventilator is part of the 510(k) approval process. This typically does not involve a physiologic assessment, but rather is a market evaluation to test customer acceptance of the product. Customer Preference Testing may be useful not only as part of the 510(k) approval process but also by providing marketing data for the manufacturer. Elements of Customer Preference Testing are:

- Device Description. This is a description of the device to be tested. The device to be tested is labeled "Investigational Device."

- Objectives of Customer Preference Testing. This is a listing of the specific questions to be answered (objectives to be met) as the result of the Customer Preference Testing. Again, the primary objective of this evaluation is to determine that the device does what it was designed to do; the objective is not safety and efficacy testing.

- Site Selection. Sites (hospitals) to participate in Customer Preference Testing are selected based upon their interest, their ability to provide the necessary facilities, their ability to provide access to the required patient types, their scientific reputation, and their willingness to comply with good and ethical clinical practices.

- Customer Preference Testing Protocol. This deals with the specifics of the evaluation plan. Details of this include evaluation-site prerequisites, patient population, and demographics, the names of the investigators, an in-service training plan, equipment requirements, duration of the evaluation, data collection tools, and the data collection plan. Although this is not a formal research study, it contains many of the elements of a research project.

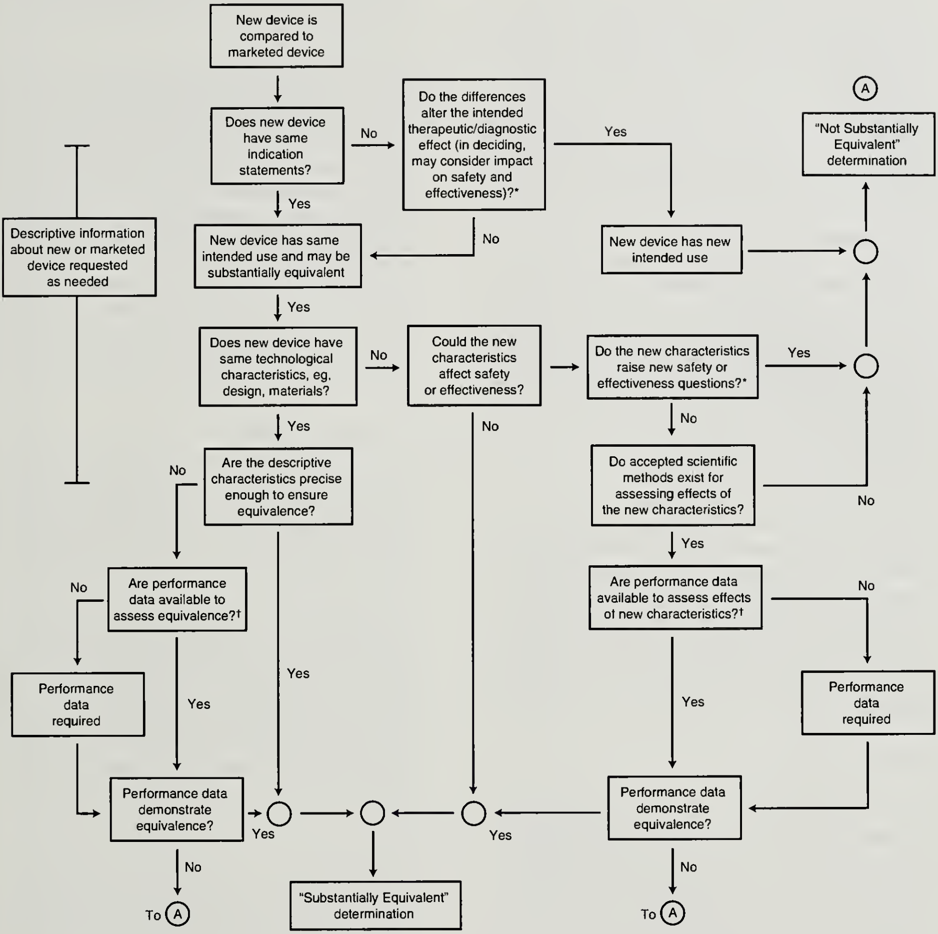
New device is compared to marketed device
Does new device have same indication statements?
No
Do the differences alter the intended therapeutic/diagnostic effect (in deciding, may consider impact on safety and effectiveness)?*
Yes
Ⓐ
"Not Substantially Equivalent" determination
Yes
Descriptive information about new or marketed device requested as needed
New device has same intended use and may be substantially equivalent
No
New device has new intended use
Yes
Does new device have same technological characteristics, eg, design, materials?
No
Could the new characteristics affect safety or effectiveness?
Do the new characteristics raise new safety or effectiveness questions?*
Yes
Yes
No
No
No
Are the descriptive characteristics precise enough to ensure equivalence?
Do accepted scientific methods exist for assessing effects of the new characteristics?
No
Yes
No
Are performance data available to assess equivalence?†
Are performance data available to assess effects of new characteristics?†
No
Yes
Performance data required
Yes
Yes
Performance data required
Performance data demonstrate equivalence?
Yes
Yes
Performance data demonstrate equivalence?
No
No
To Ⓐ
"Substantially Equivalent" determination
To Ⓐ

Fig. 1. Determining 510(k) "Substantial Equivalence:" the decision-making process. 510(k) submissions compare new devices to devices already approved and marketed. The FDA requests additional information if the relationship between marketed and "predicate" (ie, pre-Amendment or reclassified post-Amendment) devices is unclear. *This decision is normally based on descriptive information alone, but limited testing information is sometimes required. †Data may be in the 510(k) being prepared, other 510(k)s, the FDA's classification files, or the literature. (Adapted from Reference 1, with permission).

- Institutional Review Board (IRB) Approval. An evaluation involving patients requires approval by the local IRB. It is unethical to conduct any evaluation of an investigational device without IRB approval of the protocol.[3] Depending on the nature of the device, the IRB may or may not require written informed consent. The importance of following local IRB and institutional policies when conducting device evaluations cannot be overemphasized.

- Data Analysis Plan. These are the methods used to evaluate the results. Because these are not clinical trials, data analysis is often descriptive in nature.

- Written Report. When the Customer Preference Testing is complete, a written report is prepared. This report, or parts thereof, may then be submitted with a 510(k) application.

Depending upon the device, Customer Preference Testing may go through a series of iterations. It is typical that issues will arise and be addressed during Customer Preference Testing that were not anticipated by the engineers during laboratory bench testing. The prototype device is then re-engineered, and laboratory testing and Customer Preference Testing are repeated.

Respiratory therapists and other clinicians are often anxious to participate in Customer Preference Testing. When clinicians become involved in these evaluations, it is important that they appreciate the gravity of this procedure. Investigators participating in Customer Preference Testing have obligations to their patients, their institution, and the manufacturer. These evaluations must be conducted ethically and without compromise to the quality of patient care.

Pre-Market Application Approval

Unlike Class-II devices, Class-III devices require clinical studies that test safety and efficacy before FDA approval is obtained. A current example is the nitric oxide study being sponsored by Ohmeda (Madison WI). The procedure whereby Class-III devices gain FDA approval for marketing is the PMA process. The PMA procedure begins after laboratory bench and/or animal testing have been completed. The manufacturer has the ultimate responsibility for assuring that all regulations are met.

The Manufacturer

- Proposes clinical studies. These are clinical trials designed to demonstrate the safety and efficacy of the new device. These studies cannot be conducted without the approval of the FDA. Approval by the FDA to conduct clinical studies with the device does not mean that the FDA will later find these studies appropriate to demonstrate safety and efficacy. In other words, the FDA may approve clinical studies using the device but later decide that these studies were not designed appropriately. The FDA has recently begun to make it easier for manufacturers to receive FDA input early during the protocol planning process.[4] This cooperative effort between the FDA and industry should help avoid problems related to appropriate protocol design.

- Obtains an Investigational Device Exemption (IDE). Before the Class-III device can be used on patients, an IDE must be obtained by the manufacturer. The IDE essentially allows the device to be used on patients for purposes of proceeding with the PMA process. The IDE of Class-III medical devices is the counterpart to the Investigational New Drug (IND) exemption granted by the FDA to study new drugs.

- Selects qualified investigators. By their nature, Class-III devices are investigational before FDA approval. Thus, it is very important that investigators selected to conduct clinical trials for the approval of these devices be conversant with the scientific process. Individuals participating in this process will often be much more scientifically sophisticated than those who might participate in Customer Preference Testing for Class-II devices.

- Files the PMA. The results of all nonclinical and clinical studies are analyzed. These are submitted to the FDA with other materials, such as manufacturing plans, quality assurance plans, sources of suppliers, training and operational materials, and advertising literature.

Participants in Human Subject Testing

- Obtain Institutional Review Board approval. An evaluation involving patients and an IDE always requires approval by the local IRB. It is unethical to conduct any evaluation of an investigational device without IRB approval of the protocol.

- Assure appropriate monitoring of subjects. During the clinical trials, patients must be appropriately monitored, and any adverse effects must be promptly reported to the local IRB, the manufacturer, and the FDA. Serious adverse events (SAE) occurring during the investigation must be reported to the sponsor immediately by telephone and in writing within 48 hours. The sponsor must then notify the FDA within 1 week.

The FDA

- Guarantees adherence to good manufacturing practices (GMP). The FDA inspects the PMA for information related to manufacturing, quality assurance, customer service, and documentation.

- Arranges Advisory Panel review. The PMA is reviewed by an independent panel of the FDA that consists of clinical, industry, and lay persons interested in protecting the health of the public. The FDA Advisory Panel meetings are open to the public, and dates and times are published in the *Federal Register*. Even though the FDA may have approved all clinical trials to test the safety and efficacy of the Class-III device, the Advisory Panel may decide that these trials were inadequate or incorrectly designed to test safety and efficacy.

- Publishes notice of proposed approval. The proposed approval is published in the *Federal Register.* Anyone opposed to the approval has 30 days to submit objections.

- Advises the manufacturer of FDA approval. When the device is eventually approved, written notification is sent to the manufacturer, with all qualifiers, disclaimers, and rules and regulations to keep the approval valid.

This process is typically lengthy and expensive and may test the financial resources and emotional fortitude of the manufacturer. Many manufacturers may decide to forgo development of a new product because the cost of the PMA process, added to development costs, decreases the profit margin.

Case Studies

Flow-Triggering: Low Cost & Low Risk

Correct patient-ventilator interactions are important to prevent dyssynchrony, improve patient comfort, and decrease the oxygen cost of breathing. Ventilator systems that allow patient-triggering have been available since the 1960s. On this basis, the trigger mechanism of the ventilator should fit the criteria for a Class-II device, and should qualify for 510(k) approval. It could be reasonably argued that all ventilator triggers are substantially equivalent, and differ only in their electronic and pneumatic algorithms.

Until recently, ventilators have been equipped to trigger only in response to a pressure signal measured either at the proximal airway or within the ventilator. The pressure-trigger has been used to initiate assisted breaths, pressure-supported breaths, and spontaneous breaths. More recently, flow-triggered ventilator systems have become available. Studies[5-10] conducted after the commercial introduction of these systems have shown that flow-triggering is superior to pressure-triggering with respect to response time, baseline pressure drop, pressure-time product, and work of breathing. The superiority of flow-triggering is particularly important for the delivery of spontaneous breaths (eg, continuous positive airway pressure, or CPAP, and synchronized intermittent mandatory ventilation, or SIMV) but has also been shown to be useful during volume-limited and pressure-limited breaths.[10]

Intermittent mandatory ventilation (IMV) was used clinically before it became commercially available. In the early days of IMV, a typical system was jury-rigged by the clinician to provide a continuous flow through the circuit to allow spontaneous breathing between ventilator breaths. Although such a system did not allow the patient to trigger mandatory breaths, the inspiratory work of breathing for spontaneous breaths was relatively low when the flow through the system exceeded patient demand. Problems associated with these systems included improper assembly, inability of the patient to trigger mandatory breaths, and high back-pressure from the expiratory valve due to flow through the system.

Although a continuous-flow IMV ventilator was commercially available for many years (eg, Emerson IMV), most manufacturers designed demand-valve IMV systems. Demand-valve systems responded to patient effort (ie, a pressure drop in the system) to provide flow during spontaneous breathing. Because there was no continuous flow through the system, exhaled tidal volumes could be easily measured. In addition, the demand-valve system allowed mandatory breaths to be triggered by the patient (SIMV). Demand-valve SIMV systems were well accepted by many clinicians, in spite of reports in the literature of the excessive effort required to breathe from many of these systems.[11-13]

The development of flow-triggering resulted from the desire for a system that operated with a continuous flow through the circuit but allowed the patient to trigger mandatory breaths. A continuous-flow SIMV system is not practical (and perhaps not possible) with pressure-triggering of mandatory breaths. Thus, a prerequisite for a continuous-flow SIMV system was the necessity to flow-trigger mandatory breaths. Also, flow through the circuit can be reduced if the system responds to spontaneous breathing efforts (CPAP) by increasing flow as necessary to meet patient demand. The clinician's desire for a continuous-flow ventilator thus resulted in engineers' developing a continuous-flow ventilator with flow-triggering.

An example is the flow-triggering on the Puritan-Bennett 7200 ventilators. Flow-triggered prototype ventilators were developed by engineers, subjected to thorough laboratory bench testing, and had the electronic and pneumatic controls refined as necessary. Following complete validation by the manufacturer in the engineering laboratory, protocols for clinical evaluations were written. These protocols were designed only to determine whether the flow-trigger does what it is supposed to do. In other words, does the ventilator deliver flow (ie, trigger) in response to patient effort? The clinical evaluations were designed to evaluate customer preferences, and *not* to test safety and efficacy. A small number of hospitals were chosen to participate in the Customer Preference Testing. The ventilators with flow-triggering were first used with relatively healthy patients and later in increasingly difficult scenarios. Clinician evaluations were collected using a standard questionnaire. Based upon user feedback, appropriate and necessary changes were incorporated, and clinical evaluations were repeated.

Following completion of all laboratory validation testing and Customer Preference Testing, a 510(k) application was submitted. The entire process of designing, testing, and gaining approval for flow-triggering required about 16 months and 4 person-years. Flow-triggering is arguably low cost and low risk. The cost of designing and evaluating this system was relatively low, and the system uses some components and controls already present in the ventilator. Clinicians can use the flow-trigger without extensive training; in fact, manufacturer-preset default settings are often satisfactory. Finally, there is little increased risk of morbidity or mortality to the patient if flow-triggering is used incorrectly or if it should fail.

A similar case involves the development of flow synchronization by Bird Products. This device was the first to allow flow-triggered, pressure-limited, time-cycled ventilation for neonates. Impetus for the flow-triggering device came after a company employee read a newspaper article regarding a new way of ventilating infants.

The prototype being used by the physician was triggering the ventilator from impedance pneumography signals. After some discussion with the inventor, the engineering team mulled over the possibility of making the project work. After some disappointing initial studies, the engineers began to discuss alternatives to impedance pneumography as the triggering signal. During the ensuing year and a half, a neonatal flow sensor and algorithms for flow-triggering were designed.

Between 1990 and the introduction of flow synchronization on the Bird VIP ventilator, the software was continuously refined. Clinical trials demonstrating the safety of the device were accomplished as well as Customer Preference Testing. Bench evaluations of each of the modifications suggested by clinicians were undertaken prior to additional clinical evaluations.

The development of the flow-triggering system is estimated to have cost $800,000. The 510(k) review process was completed in 12 months. Like the previous example, it could be argued that flow-triggering for neonates is low risk. However, due to the inherent difficulties associated with sensing respiratory efforts of neonates and the potential deleterious effects of failure to detect breathing, this type of flow-triggering might be considered moderate risk. The issue of cost is based on perspective. At a cost of $800,000, most clinicians would consider this high cost. However, this would typically be considered moderate cost by most manufacturers. This may serve to demonstrate the dilemmas facing the FDA. Within the discipline of mechanical ventilation, the same design (flow-triggering) might be considered low or moderate risk depending on other circumstances. From the perspective of the manufacturer, the same device—the flow-trigger—might be considered low or moderate cost.

Pressure-Control Ventilation: Moderate Cost & Moderate Risk

Pressure-limited ventilation has been available since the earliest days of mechanical ventilation. The Bird and Bennett ventilators commonly used in the 1960s and 1970s were pressure-limited ventilators. Pressure ventilators of that era were pressure-cycled rather than pressure-limited and were not sufficiently sophisticated to ventilate critically ill patients whose impedance was high. Because it was difficult to adequately ventilate patients with high and changing pulmonary impedance using these ventilators, they were virtually abandoned in favor of volume ventilators. For neonates, however, time-cycled pressure-limited ventilation became standard practice. In recent years, interest in pressure ventilation of adults has been renewed due primarily to a legitimate concern for the effects of high airway pressures on localized overdistention within the lungs.[14]

Until the mid-1980s, pressure ventilators did not have sophisticated feedback control for gas delivery in a pressure-limited, time-cycled manner. Engineering of a pressure-limited ventilator required development of algorithms for flow delivery that resulted in the constant-pressure and decelerating flow pattern typical of pressure ventilation. The electronic and pneumatic controls required for this inspiratory pattern were much different from those previously used for volume-limited or pressure-cycled ventilators.

An example is provided by the pressure-control function of the Puritan-Bennett 7200 ventilator. Design of a pressure-limited and time-cycled mode of ventilation required decisions related to the ventilator-clinician interface. For example, inspiratory time can be determined by setting it directly, by setting an inspiratory-expiratory time ratio, or by setting an inspiratory time fraction. Further, decisions regarding the pressure target were necessary—the pressure setting could be the absolute peak airway pressure desired or the pressure above PEEP. These issues were resolved through conferences between clinicians and engineers and through bench testing of electronic control systems and pneumatic gas-delivery systems.

The testing and development of pressure ventilation were more involved than were testing and development of flow-triggering. Pressure ventilation was conceptually more difficult for clinicians to use. Clinicians' understanding of pressure ventilation required considerable effort. As a result, Customer Preference Testing was more involved with pressure ventilation. Not only did clinicians need to evaluate the pressure ventilation capability of the ventilator, but they also needed to learn a fundamentally different concept of mechanical ventilation of adult patients. As a result, multiple iterations of Customer Preference Testing were required for pressure ventilation.

A 510(k) application was submitted after completion of laboratory testing and Customer Preference Testing. The entire process of designing, testing, and gaining approval for pressure ventilation required about 30 months and 4 person-years. Pressure ventilation can be classified as moderate cost and moderate risk. The cost and time for development of the pressure-limited ventilation system were greater than they had been for a technique such as flow-triggering. The moderate risk of a pressure-limited ventilation system is related to clinician understanding (or misunderstanding) of the use of the method. Misuse of pressure-limited ventilation can produce moderate patient risk related to inappropriate settings of pressure and inspiratory time by clinicians who are unfamiliar with the method.

Clinical evaluations of pressure ventilation have all occurred after ventilators that incorporated this method became commercially available.[15,16] Considerable confusion remains regarding the usefulness of this mode. Although improved oxygenation has been reported when patients were switched from volume to pressure ventilation, it remains unclear whether those improvements were due to changes in mean airway pressure, auto-PEEP levels, inspiratory time, or inspiratory flow pattern.[17] Controlled clinical trials are still needed to resolve this issue. It is our bias that the benefit of pressure control may be the avoidance of high peak alveolar pressure and the associated overdistention. However, this remains unproven and is purely speculative at this time.

Volume-Assured Pressure Support: Low Risk & Moderate Cost

The issue of patient-ventilator synchrony and concern about the work of breathing during assist-control ventilation has led to several recent modifications of existing modes. These include volume-assured pressure support (VAPS), pressure augmentation, and pressure-regulated volume control.[18]

VAPS was introduced by a physician and engineer from Brazil.[19] It is currently available on the Bird 8400STi and performs two functions. In the assist-control mode, each breath begins like a pressure-control breath (rapid initial flow) to help reduce the work of breathing. However, unlike a pressure-control breath, the volume delivered is constant. Because the flow is at a maximum at the beginning of the breath and varies with patient demand, this mode may be useful for patients with frequently changing ventilatory demands.[20]

In the pressure-support mode, VAPS allows normal pressure-support function, unless the delivered volume falls below a threshold set by the clinician. If this occurs, the ventilator allows pressure to increase as flow is delivered to maintain the set tidal volume. Inconsistent tidal volume delivery is a frequent criticism of pressure-support ventilation, and the VAPS mode appears to be an answer to this problem.

Initial bench testing and Customer Preference Testing were accomplished, design changes suggested, and modifications made. During the 510(k) review process, the FDA implemented new regulations regarding electromagnetic interference and software testing. This required repeated modifications to the 510(k) submission. After nearly a year, a similar device was 510(k) approved by the FDA. Bird Corporation then used this as a predicate device claiming "substantial equivalence." After a total of 15 months, VAPS was approved with no clinical data included in the application. Claiming equivalence to a recently approved device negated the need for actual patient testing.

High-Frequency Jet Ventilation: High Cost & High Risk

There has been interest in high-frequency ventilation techniques for many years stemming from the desire to ventilate the lungs of patients at low tidal volumes to avoid the overdistention, acute lung injury, and barotrauma associated with high alveolar pressures.[21,22]

Perhaps the first mechanical ventilator to be subjected to the entire PMA process was the Bunnell Life Pulse, a neonatal jet ventilator. FDA approval to conduct the clinical trials began in October 1981 for any condition that failed to respond to conventional neonatal ventilation. An attempt was made to recruit as many sites as possible, but the FDA had a limit of 20 sites and considered more than this as commercialization. Each clinical site paid for the investigational device and supplies. The manufacturer could exercise only limited control of the protocols, and thus protocols differed at each site.

By mid-1985, data were collected on over 150 babies at 5 hospitals. It was decided to focus on those with severe respiratory distress syndrome (RDS) complicated by pulmonary air leaks. The full PMA was submitted in August 1985. In November 1985, the PMA was rejected with 12 administrative deficiencies. The principal criticism was that a randomized controlled study had not been conducted. Bunnell responded in writing to the 12 deficiencies and requested that the application be reviewed by an FDA Advisory Panel.

In June 1987, the PMA was scheduled for a hearing before the FDA Advisory Panel. However, the FDA's statisticians refused to accept the data because there was no suitable control group. The Advisory Panel suggested that the suitable control group requested by the FDA was either impossible or impractical and specified the additional data necessary to gain approval. By November 1987, an additional 108 patients were added to the original 92 babies with severe RDS complicated by pulmonary air leak. These data were presented to the FDA Advisory Panel, who suggested that the device could be approved with only minor modifications. On June 30, 1988—almost 7 years after clinical trials were initiated, the FDA approved the jet ventilator for marketing.

Not counting hospital personnel time and expenses to conduct the clinical trials (hospitals paid for the ventilators and supplies, and donated clinical time), an estimated 20-30 person-years were required to gain FDA approval of this ventilator. The personnel expenses charged to this project were about $2,000,000.

Charting a parallel course, Dr Forrest Bird filed for an IDE and PMA in 1980 for a family of high-frequency devices based on his theory of intrapulmonary percussive ventilation (IPV). The earliest devices were similar to high-frequency jet ventilators. However, using a venturi and all pneumatic components, Bird was able to create a type of pressure-limited ventilation wherein the pressure limit was reached by using small high-frequency bursts of gas.

During the clinical investigations, all investigators were provided with ventilators and disposables at no charge. All clinical trials were performed without additional charge to the company, although in the end, clinical sites were given equipment to continue further research. Bird had been convinced initially that acquiring a PMA was the approval of choice. During the decade of trials prior to approval, Bird met with FDA on numerous occasions. In his estimation, the biggest problem at FDA was that the agency was given too difficult a charge by Congress and too few resources to accomplish the task.

In the end, Bird was granted a 510(k) by demonstrating that a Bird Mark II (the timing mechanism from the babyBird) was capable of providing ventilator rates in excess of 150 breaths/min. In this case, substantial equivalence was established using prior art. It has been estimated that the cost associated with FDA review for final approval of the family of high-frequency devices was around $500,000.

High-frequency ventilation is now well accepted in neonatal respiratory care,[23,24] and applications of high-frequency ventilation have been described in adults.[25-30] We believe that most clinicians would agree that high-frequency ventilation is high risk and high cost. It is completely unlike conventional ventilation; it is likely to cause harm if it is not effective; and it is costly in terms of hardware, personnel training, and the PMA process. Regardless of whether one supports the use of high-frequency ventilation, a number of issues are raised by the Bunnell and Bird experiences. We believe the following to be true:

- The process is ambiguous. The PMA process does not seem well-defined, expectations are not clear, and little constructive feedback is provided.

- The process is not user friendly, and because the process is not facilitated, the appearance of 'stone-walling' is presented.

- The process is not expeditious. Approval of a device such as a high-frequency ventilator takes about 7 years. During this time, there are long lag times between submission of PMA materials and official action or feedback.

- Approval of clinical trials is separate from the PMA process. The FDA may approve clinical trials using the investigational device; however, the approved clinical trials may not be found appropriate by the FDA to authorize marketing.

- What constitutes an acceptable clinical trial for FDA approval is unclear. This should be clarified early in the design of clinical trials. Considerable time and resources are wasted if the FDA finds that the results of clinical trials are inadequate to permit marketing. The ideal design would be a randomized controlled clinical trial with appropriate statistical power and an appropriate outcome, such as improved morbidity or mortality. Cost should also be considered (eg, ventilator days, ICU days, hospital stay). In other cases, randomized trials may be unnecessary or unethical. In some cases, a succession of clinical trials may be necessary, beginning with physiologic outcomes and progressing to other more important outcomes, such as mortality.

- The process is expensive. The PMA process is expensive, particularly in relation to clinical trials. This expense is often assumed by the manufacturer, who then passes the cost on to the consumer. In some cases, the manufacturer funds the clinical trials by selling investigational devices to the investigating sites.

- The appropriate role of the inventor or manufacturer is unclear. The inventor or manufacturer is usually intimately involved in the clinical trials required as part of the PMA process. Because there is the eventual possibility of financial gain, the issue of conflict of interest arises. A tug-of-war can develop between the inventor as proponent and the FDA as skeptic. A solution would be to fund independent clinical trials, but this may be neither practical nor possible. It is not reasonable to expect academic centers to support clinical trials without remuneration because investigators in academic centers depend on funding to conduct such trials.

- The process is intimidating. Our personal observations suggest that the FDA intimidates all manufacturers of medical devices, whether approval is sought through the 510(k) process or the PMA process. The medical device industry operates in constant concern related to the FDA. Research and development efforts of industry are always governed to some extent by FDA-related apprehension, resulting in guarded creativity and increased development costs.

Some Questions That Arise

When Does a Modification Require Approval?

Minor device alterations may be needed after FDA approval to market a device has been received. When such modifications require a new 510(k) or PMA has not been made entirely clear. Manufacturers usually avoid modifications that will require a new FDA application for approval. A new FDA application is generally required if modifications of the device result in a change in "form, fit, or function."[1] For minor modifications, manufacturers usually file internal documentation to justify that there was no change in form, fit, or function. In that way, a new FDA application may be avoided. However, there is always the possibility that the FDA will challenge that decision, particularly if a device malfunction is reported. How a manufacturer deals with issues such as this relates to the FDA's judgment of "good manufacturing practices." A 510(k) may not be necessary if the following criteria are met: there is no intent to change device specifications, well-accepted testing procedures assure that the original specifications are met, and the original specifications were adequate to assure that conformance to specifications guarantees that the device has not changed. Examples of design changes that require a new 510(k) include a change that may result in breakage, a change in material to one that is not biocompatible, or a change to a component of lesser strength than the original component. The more critical the nature of the modification and the more complex the evaluation of the modification, the more likely it is that a 510(k) will be required.

When Will the FDA Prosecute?

The FDA is authorized to criminally prosecute medical device manufacturers (as well as individuals) for the commission of acts prohibited by the Medical Device Amendment Act.[1,2] However, it appears that few manufacturers or individuals are ever prosecuted. The FDA has a policy of incremental enforcement. A warning letter is issued for those violations that do not present danger to the health of the public, that are inadvertent, and that are likely to be corrected upon request by the FDA. Larger problems may result in seizure, injunctive action, detention, or mandatory recalls. Prosecution is reserved for serious disregard of the public health, fraud, or intentional violations of the Medical Device Amendment Act.

Where Is Reality?

A delicate balance is needed to protect the interests of the patient, the inventor and/or manufacturer, and the tax payer (who funds the FDA). No clinician is tolerant of an unsafe or ineffective device, but, how much should we be willing to spend; and, how much testing should be required to determine that a device is safe and effective? As clinicians, we typically have little appreciation for the FDA-approval process. Many of the devices that we commonly use were FDA approved as the result of the 510(k) process. This is puzzling when one considers that virtually no device used today resembles devices used before 1976.

As clinicians, we may be asked to participate in Customer Preference Testing or clinical protocols involving investigational devices. These activities should not be taken lightly. It is extremely important that the necessary institutional approvals be obtained and that the patient and the institution be appropriately protected. In virtually all cases, approval of the IRB will be required. The temptation to naively use an investigational device without proper authorization must be avoided.

We believe that the FDA-approval process definitely affects the practice of respiratory care. It affects innovation; it affects how new devices are used; and it affects the costs of new devices. An appropriate balance between innovation and regulation is needed. No one wants approval of devices that are unsafe; likewise no one wants to be deprived of devices that are effective but do not meet the rigors of the regulatory process. Those who implement the regulatory process try to avoid approving unsafe devices. However, it is unfortunate but true that decreasing the likelihood of approving an unsafe device increases the probability of failing to approve a device that is safe and effective.

All medical devices have some risk—a risk-free device does not exist. What is important is that the benefit of the device outweigh the risk. If the risk threshold is too low, potentially beneficial devices may not be approved. The question then becomes, who should determine benefit (ie, effectiveness)? Should this be a regulatory agency like the FDA or should this be clinicians and/or industry?

It has been estimated that the majority of medical device manufacturers have 50 or fewer employees, and that many if not most innovations come from these manufacturers. What happens to innovation if these small manufacturers cannot afford regulation? If less innovation occurs, is this good for respiratory care?

Is the Review Process Fair?

Human nature dictates that two people given the opportunity to subjectively review the same material may come to two different conclusions. All authors can attest to the truth of this statement. In order to prevent biased review, manuscripts submitted to some journals are blinded, ie, the reviewer does not know who authored the manuscript. The same is not true for FDA reviews. Some manufacturers have alluded to unfair treatment by the FDA.

In a recent court case,[30,31] the FDA review process was put to the test. RS Medical manufactured and marketed a muscle stimulator. The company believed that they had an unfavorable status with the FDA and that this status would result in a biased and unfair review. In order to test this belief, RS Medical sent two identical 510(k) applications to the FDA, one under the company's name and one using the name of a consultant not previously affiliated with the company.

RS Medical filed the 510(k) application on January 30, 1992, and the consultant filed the application on February 10, 1992. The technical documentation was identical. The consultant's application was approved on April 23, 1992, after several questions had been answered. The initial RS Medical application review process was denied on January 28, 1993. This occurred despite the fact that the submissions were identical. The company sued the FDA, and the court concluded that the FDA's reasons for disapproval were "unreasonable and arbitrary," and further ruled that the FDA's actions constituted "bad faith."[30,31]

To be fair, any two reviewers operating with the expert advice of consultants may not come to the same conclusion. When patient safety is at the heart of the issue, the reviewer will always err on the side of "do no harm." However, this case reveals the difficulties and inequities created by the current review process. Both the FDA and the manufacturer must work within the constraints of impending legal action, and neither can afford to make a mistake.

One answer to this problem may be the introduction of user fees. Under such a system, the manufacturer would pay for the review as an application fee. This is coupled with new FDA efforts to work with manufacturers early in product development to help alleviate some of the tension between the two camps. Phelps[30] has suggested that the user fee will allow the FDA to perform its job more effectively and that we cannot expect the FDA to be both " scientist and policeman." Unfortunately, user fees increase the costs of product development and may discourage innovations by small companies that cannot afford user fees.

Who Bears the Cost?

The price of regulation is passed on to the consumers who paid for it initially (taxes to support FDA). The exact amount passed on to the customer because of regulatory documentation and testing is unknown, although several manufacturers have suggested it is on the order of 10-15%. These costs are associated with functional and software testing and the required documentation. Figure 2 shows the number of pages of documentation submitted by Bird Products per year with 510(k) submissions. The recent software regulations have caused an exponential rise that only promises to increase. These growing numbers of pages are the result of engineers' performing and recording the required testing. Every additional page means additional product costs.

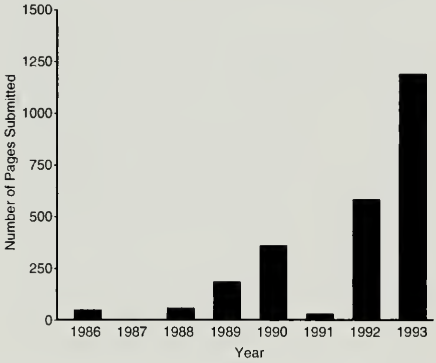

Fig. 2. Number of pages submitted with 510(k) applications by Bird Products Corporation over the past 8 years. (From corporate records, courtesy of Bird Products Corporation).

Of course from the FDA side, additional pages mean additional work and longer review times. In the 1993 ODE report,[32] this problem was highlighted. In 1992, the average FDA review time for a PMA was 146 days; in 1993, it was 328 days. The average time for approval of a PMA was 437 days. In 1993, the average review time for a 510(k) submission was 195 days, up nearly 50% from 1992.

These time increases are attributed to the new GMP rules and changes in FDA regulations. Figure 3 shows the average FDA review time for a 510(k) submitted by Bird Products during the past several years. Prolonged reviews increase the amount of time it takes for a product to come to market and likewise increase costs.

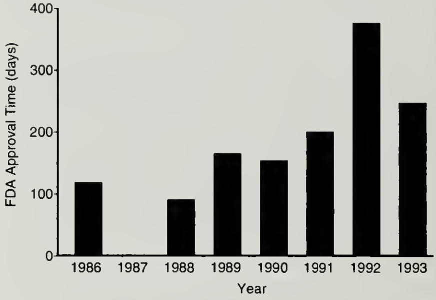

Fig. 3. Time from submittal to approval of 510(k) applications by Bird Products Corporation over the past 8 years. (From corporate records, courtesy of Bird Products Corporation).

In Conclusion

There is no doubt that the problem of how best to introduce and test innovations for mechanical ventilation is multifaceted. The FDA is expected to provide the American people with 100% safety in a prompt and inexpensive manner. Manufacturers are likewise expected to produce safe, economical, and effective devices. However, the current burden on the FDA and lack of funds from Congress make this an implausible combination. It appears clear that the review process and the degree of documentation require streamlining.

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REFERENCES

1. Grahm A, Branson RD. Approval and surveillance of medical devices. In: Branson RD, Hess DR, Chatburn RL. Respiratory care equipment. Philadelphia: JB Lippincott, 1995.
2. Public Law 101-629. 104 STAT.4511. Safe medical devices act of 1990. Nov 28, 1990. H.R. 3095. Health care. 21 USC 301 note.

3. Food and Drug Administration, Department of Health & Human Services. FDA IRB information sheets. February 1989:73.
4. Food and Drug Administration. Medical devices and radiological health. FDA Internet: http://www.fda.gov/opacom/hpcdrh.html, March 13, 1995.
5. Servant GM, Nicks JJ, Donn SM, Brandy KP, Lathrop C, Deckert RE. Feasibility of applying flow synchronized ventilation to very low birth weight infants. Respir Care 1992;37(3):249-253.
6. Branson RD, Campbell RS, Davis K, Johnson DJ. Comparison of pressure and flow triggering systems during continuous positive airway pressure. Chest 1994;106:540-544.
7. Sassoon CS, del Rosairo N, Fei R, Rheeman CH, Gruer SE, Mahutte CK. Influence of pressure- and flow-triggered synchronous intermittent mandatory ventilation on inspiratory muscle work. Crit Care Med 1994;22(12):1933-1941.
8. Nishimura M, Hess D, Kacmarek RM. The response of flow triggered demand valve systems in infant ventilators. Am J Respir Crit Care Med 1995 (in press).
9. El-Khatib M, Chatburn RL, Potts DL, Blumer JL, Smith PG. Mechanical ventilators optimized for pediatric use decrease work of breathing and oxygen consumption during pressure-support ventilation. Crit Care Med 1994;22:1942-1948.
10. Giuliani R, Mascia L, Recchia F, Caracciolo A, Fiore T, Ranieri VM. Patient-ventilator interaction during synchronized intermittent mandatory ventilation. Effects of flow triggering. Am J Respir Crit Care Med 1995;151(1):1-9.
11. Christopher KL, Neff TA, Bowman JL, Eberle DJ, Irvin CG, Good JT Jr. Demand and continuous flow intermittent mandatory ventilation systems. Chest 1985;87(5):625-630.
12. Viale JP, Annat G, Bertrand O, Godard J, Motin J. Additional inspiratory work in intubated patients breathing with continuous positive airway pressure systems. Anesthesiology 1985;63(5):536-539.
13. Katz JA, Kraemer RW, Gjerde GE. Inspiratory work and airway pressure with continuous positive airway pressure delivery systems. Chest 1985;88(4):519-526.
14. Slutsky AS. Mechanical ventilation: American College of Chest Physicians consensus conference. Chest 1993;104(6):1833-1859.
15. Lessard MR, Guerot E, Lorino F, Lemaire F, Brochard L. Effects of pressure control with different I/E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress. Anesthesiology 1994;80(5):983-991.
16. Abraham E, Yoshihara G. Cardiorespiratory effects of pressure controlled inverse ratio ventilation in severe respiratory failure. Chest 1989;96(6):1356-1359.
17. Mang H, Kacmarek RM, Ritz R, Wilson RS, Kimball WP. Cardiorespiratory effects of volume- and pressure-controlled ventilation at various I/E ratios in an acute lung injury model. Am J Respir Crit Care Med 1995;151(3, Part 1):731-736.
18. Kacmarek RM, Hess D. Basic principles of ventilator machinery. In: Tobin MJ. Principles and practice of mechanical ventilation. New York: Mc-Graw Hill, 1994.
19. Amato MBP, Barbas CS, Bonassa J, Saldiva PH, Zin WA, de Carvalho CR. Volume-assured pressure support (VAPSV): a new approach for reducing muscle workload during acute respiratory failure. Chest 1992;102(4):1225-1234.
20. Haas CF, Branson RD, Folk LM, Campbell RS, Wise CR, Davis K, Deckert RE, Weg JG. Patient determined inspiratory flow during assisted mechanical ventilation. Respir Care 1995;40(7):716-721.
21. MacIntyre NR. High-frequency ventilation. In: Tobin MJ. Principles and practice of mechanical ventilation. New York: Mc-Graw Hill, 1994.
22. Branson RD. High-frequency ventilators. In: Branson RD, Hess DR, Chatburn RL. Respiratory care equipment. Philadelphia: JB Lippincott, 1995.
23 Pfenninger J, Minder C. Pressure-volume curves, static compliances and gas exchange in hyaline membrane disease during conventional ventilation and high frequency ventilation. Intensive Care Med 1988; 14(4):364-372.
24. HIFO Study Group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. J Pediatr 1993;122(4):609-619.
25. Gallagher TJ, Boysen PG, Davidson DD, Miller JR, Leven SB. High frequency percussive ventilation compared with conventional mechanical ventilation (abstract). Crit Care Med 1985;13:312.
26. Barrette RR, Hurst JM, Branson RD, Davis K. A comparison of conventional mechanical hyperventilation with two forms of high-frequency ventilation for the control of intracranial pressure in closed head injury. Respir Care 1987;32(9):733-740.
27. Hurst JM, Branson RD, Davis K Jr. High-frequency percussive ventilation in the management of elevated intracranial pressure. J Trauma 1988;28(9):1363-1367.
28. Hurst JM, Branson RD, Davis K, Barrette RR, Adams KS. Comparison of conventional mechanical ventilation and high frequency ventilation: a prospective, randomized trial in patients with respiratory failure. Ann Surg 1990;211(4):486-491.
29. Gluck E, Heard S, Patel C, Mohr J, Calkins J, Fink MP, Landow L. Use of ultrahigh frequency ventilation in patients with ARDS. A preliminary report. Chest 1993;103(5):1413-1420.
30. Phelps JR, Bad-faith reviews: The RS medical case. Medical device & diagnostic industry 1994(Sept):30-32.
31. International Rehabilitative Services Inc, Debra RS Medical v. Kessler (Civil No. SA-93-CA-0242: WED. Tex, March 10, 1994).
32. U.S. Department of Health and Human Services. Office of device evaluation annual report, 1993.

Efficacy Assessment Criteria Based on Risk and Cost

Neil R MacIntyre MD

I. Introduction
II. Innovation Claims & Levels of Efficacy Testing
  A. Level 1—Engineering & Clinical Performance Assessment
  B. Level 2—Physiologic Assessment
  C. Level 3—Clinical Outcome Assessment
III. Selecting Claims & Consequent Level of Assessment
  A. Risks
  B. Costs
IV. Application
V. Conclusions

Introduction

Innovations in mechanical ventilation can come both from new engineering designs and from new applications of existing designs.[1,2] New designs can range from simple features, such as flow-triggering and inspiratory pressure-slope adjusters to completely new approaches to ventilatory support such as high-frequency and liquid ventilation. Examples of new applications include inverse-ratio ventilation, stand-alone pressure-support ventilation, and applied end-expiratory positive pressure (PEEP) to reduce the inspiratory triggering load induced by air trapping in obstructive lung disease. Regardless of the innovation, the claims of benefit by the manufacturer or the clinician should be verified through efficacy assessment.

Innovation Claims & Levels of Efficacy Testing

An innovation is designed to provide a benefit, and establishing the presence of that benefit provides the basis for claim by the manufacturer or clinician-innovator. This claim is usually one of three types: (a) engineering—a claim stating that the innovation improves technical performance, ease of operation, or cost of operation; (b) physiologic—a claim stating that the innovation improves an intermediate physiologic variable in the patient, such as gas exchange or patient work; (c) outcome—a claim stating that the innovation affects an important clinical outcome. Because efficacy assessment focuses on the claim, there are also three levels of efficacy assessment criteria. These levels differ in their cost, complexity, and relationship to the actual innovation's function (Table 1).

Level I: Engineering & Clinical Performance Assessment

Engineering testing involves specific laboratory evaluation of an innovation's performance using computer or mechanical models. With this approach, engineering specifications can be validated and reliability can be established. A clinical performance evaluation provides a similar function because it focuses on the specific performance characteristics of the innovation in the clinical setting. Subjective impressions of the innovation may also be determined. This form of evaluation is inexpensive and innovation specific but does not provide information to evaluate any substantial clinical benefits. Clinical efficacy can only be inferred from this form of assessment. Also, unanticipated safety issues cannot be assessed.

Level II: Physiologic Assessment

This testing considers clinical variables that can be readily assessed as the innovation is applied and used. Examples

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Table 1. Efficacy Assessment Criteria

	Criterion Type	Cost/Complexity	Test Results Assess Clinical Outcome	Test Results Directly Attributed to the Innovation's Function
I.	Engineering, clinical technical performance	Low	No	Yes–by definition
II.	Physiologic variable	Moderate	Outcome effect is inferred	Yes–if criterion is focused on expected benefits
III.	Clinical outcome	High	Yes–by definition	A technical innovation may have limited impact on overall clinical outcome

relative to mechanical ventilation include gas exchange, respiratory mechanics, patient work, and cardiovascular function. The specific selection is usually based on anticipated mechanisms of benefit or risk and should also have some reasonable link to outcome (ie, an outcome "surrogate").[3,4] These assessments are generally more expensive because clinical protocols are required. Any effect on clinical outcome, however, can only be inferred from the physiologic variables assessed. Moreover, long-term safety issues cannot be addressed.

Level III: Clinical Outcome Assessment

This testing is conducted over longer periods of time to determine whether an innovation actually has an impact on important clinical outcomes.[3,5] While the most important outcome is a change in attributable deaths (ie, an increase or decrease in mortality), other clinically relevant outcomes could be a lower complication rate or less ventilator time required.[3,5] The advantage of this type of assessment is that an important clinical outcome can be strong justification for adoption or rejection of the innovation. However, these assessments are complex and expensive, usually involving randomized clinical trials. Moreover, because mortality and other important clinical outcomes are affected by many other factors, a beneficial effect of the innovation may not be detectable in even a relatively large clinical trial.

Selecting Claims & Consequent Level of Assessment

As noted earlier, claims and the consequent level of efficacy assessment can range from the simple bench test to complex clinical trials. Choosing the appropriate claim and assessment level should depend both on the perceived benefit and on the risks and costs of the innovation. The innovator's desired advertising and labeling statements dictate to a large extent the specific level of claim and efficacy assessment required. Risks and costs, however, are equally important because they dictate the minimum level of claim and efficacy assessment that is required.

Risks

Regulatory approval and clinician liability protection depend upon assessing a claim for efficacy with respect to the potential risk.[6-10] The risk of the innovation is the risk remaining when the risk of 'standard' mechanical ventilatory support has been removed. Clinicians may not anticipate every risk prior to innovation evaluation, although experienced clinicians should be able to foresee most of them.

Risk can be categorized in a variety of ways but a three-level approach is a practical way that can be used by regulatory agencies. (Personal communication, Douglas DeVries, Bird Products Corp, from FDA Guidelines, April 1995.) With this approach, risks are categorized as minor (harm possible, but morbidity unlikely to change), moderate (harm possible, but mortality unlikely to change), and major (harm possible and mortality could be affected). The minimal level of claim and efficacy assessment required should be related to this risk (Table 2). For instance, an innovation designed to produce a technical performance improvement, a human interface improvement, or a cost improvement need only be evaluated for engineering specification if risks are virtually nonexistent or minor. An innovation designed to provide a benefit such as improved oxygenation or reduced ventilation pressures could be appropriately evaluated with only physiologic testing if the risks were moderate. However, a claim with appropriate efficacy testing for an important clinical outcome benefit would be necessary if the innovation might be associated with major risk.

Table 2. Efficacy Criteria Selection for Regulators

Risk	Claims/Efficacy Criteria
Minor	Engineering claims with Level-I efficacy criteria*
Moderate	Physiologic claims with Level-II efficacy criteria
Major	Clinical outcome claims with Level-III efficacy criteria

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* Levels are identified in Table 1.

Costs

The cost of the innovation, although not important in establishing risk-benefit ratios for regulatory and liability concern,[11] is important in establishing the appropriateness of reimbursement and, thus, widespread clinical use.[12-14] This cost is the ultimate cost passed on to the patient/payer and includes not only the equipment itself but also the cost of maintenance, supplies, personnel, and liability protection. From the reimbursement perspective, a low-cost innovation might be justified by demonstrating only engineering advantages, subjective preferences, clinical experience, or even theoretical considerations. On the other hand, an expensive innovation, even though it satisfies regulatory concerns with only engineering or physiologic assessment, should require legitimate clinical outcome data to justify its widespread application. With regard to reimbursement, then, efficacy must be assessed relative to cost.

Categorizing costs is difficult, but many institutions use a three-level system to determine the level of approval necessary for an innovation to be purchased (Table 3). For example, an innovation's cost would be considered low if the budgetary impact is < 1%, moderate if the budgetary impact is 1-5%, and high if the budgetary impact is > 5%. With this cost structure in force, use of low-cost innovations could be reimbursed with only engineering claims and efficacy assessment, use of innovations of low or moderate cost could be reimbursed with physiologic claims and efficacy assessment, and high-cost innovations could be reimbursed only with outcome claims and efficacy assessment. Innovations that satisfy regulatory or liability concerns with lower-level efficacy assessment may thus have to use a higher-level efficacy assessment to justify reimbursement.

Table 3. Efficacy Criteria Selection for Payers

Cost	Claims/Efficacy Criteria
Low	Engineering claims with Level-I efficacy criteria*
Moderate	Physiologic claims with Level-II efficacy criteria
High	Outcome claims with Level-III efficacy criteria

* Levels are identified in Table 1.

Applications

To illustrate the range of risks and costs associated with recent innovations in mechanical ventilation, I surveyed members of the of the RESPIRATORY CARE Editorial Board (n = 8) in January 1994. They were asked to come to consensus on the categories of risk and costs of a number of recent innovations, using a three-level scoring system. The results are presented in Table 4 and show the range of risks and costs associated with these innovations.

Table 4. Estimated Risk and Cost Categories of Several Recent Innovations (Survey of RESPIRATORY CARE Editorial Board)

Innovation	Consensus Opinion Risk	Cost
Pressure-slope adjustment	Minor	Low
Inverse-ratio ventilation	Major	Low
Tracheal gas insufflation	Moderate	Moderate
Proportional-assist ventilation	Moderate	Moderate
Extracorporeal respiratory support	Major	High
Flow-triggering	Minor	Low
High-frequency ventilation	Major	High
Esophageal pressure monitoring	Minor	Moderate

Conclusions

Efficacy assessment is required for all innovations to satisfy clinical, regulatory, liability, and reimbursement concerns. Efficacy assessment can be done in a number of ways using a variety of criteria that can range from the simple and inexpensive engineering test to the complex and expensive randomized clinical trial. The purpose of efficacy assessment is to validate a claim through hypothesis testing. This claim for the innovation is the basis for the 'ultimate' marketing of the innovation, either by the manufacturer or by the clinician-innovator. Efficacy assessment for a claim that an inexpensive device has a faster response time needs only an engineering test to validate it, whereas a claim that an expensive innovation reduces mortality needs a clinical trial. In selecting the minimal claim and the assessment required, risk and cost must be considered. Risk assessment must be used to evaluate the claim for regulatory and liability concerns. Cost assessment must be used to evaluate the claim for payer concerns.

REFERENCES

1. Roberts EB, Levy RI, Frankelstein SN, Moskowitz J, Sonolik EJ. Biomedical Innovation. Cambridge: MIT Press, 1981.
2. Health Care Technology Institute. The dialogue of device innovation: an overview of the medical technology innovation process. Geigle & Associates. November 1993.
3. Terrin ML. Efficient use of endpoints in clinical trials: a clinical perspective. Stat Med 1990(1-2);9:155-160.
4. Boisel JP, Collet JP, Moleur P, Haugh M. Surrogate endpoints: a basis for a rational approach. Eur J Clin Pharmacol 1992;43:235-244.
5. Dellinger RP. Clinical trials in ARDS. New Horizons 1993;1:584-592.
6. Benson JS. A look at the progress of the Food and Drug Administration's medical device program. Food Drug Cosmet Law J 1985;40:95-102.
7. FDA: Potential harm is key to significant risk decisions. Devices Diagn Lett 1986;13:1-2.
8. Kessler DA, Pape SM, Sundwall DN. The federal regulation of medical devices. N Engl J Med 1987;317(6):357-366.
9. Sherertz RJ, Steed SA. Medical devices: significant risk vs nonsignificant risk. JAMA 1994;272(12):955-956.
10. Technology assessment task force of the Society of Critical Care Medicine. A model for technology assessment applied to pulse oximetry. Crit Care Med 1993;21(4):615-624.
11. Bucci VA, Reiss JB. Technology assessment of medical devices under Medicare: who should examine "safety and effectiveness?" Food Drug Cosmet Law J 1985;40:445-455.
12. Anderson G, Steinberg E. To buy or not to buy: technology acquisition under prospective payment. N Engl J Med 1984;311(3):182-185.
13. Kane NM, Manoukian PD. The effect of the Medicare prospective payment system on the adoption of new technology: the case of cochlear implants. N Engl J Med 1989;321(20):1378-1383.
14. Trajtenberg M. Economic analysis of product innovation: the case of CT scanners. Cambridge: Harvard Univ Press, 1990.

Using Physiologic End Points To Assess Innovations in Mechanical Ventilation

Martin J Tobin MD, Amal Jubran MD, Franco Laghi MD, and Rajiv Dhand MD

I. **Introduction**
II. **Measuring Physiologic End Points**
  A. **Dyspnea**
  B. **Work of Breathing**
  C. **Pulmonary Gas Exchange**
  D. **Muscle Fatigue**
  E. **Issues in Study Design**
III. **In Summary**

Introduction

In the past, many features on mechanical ventilators were introduced by manufacturers without rigorous assessment of their tolerance by patients or their physiologic consequences. We believe that all innovations should be subjected to certain minimal evaluation before their introduction into clinical practice. This evaluation should focus on intermediate end points based on the goals of ventilator support, namely relief of respiratory distress, reduction in the work of breathing, improvement in pulmonary gas exchange, and reversal of respiratory muscle fatigue.[1]

Measuring Physiologic End Points

Dyspnea

Although reduction in respiratory distress is one of the major goals of mechanical ventilation, it is interesting that few investigators have examined its efficacy in this regard. In a systematic study in ventilator-dependent patients, Knebel et al[2] found that dyspnea remained largely unchanged as the levels of pressure support ventilation (PSV) and intermittent mandatory ventilation (IMV) were each varied. This is surprising because investigators have convincingly demonstrated large reductions in the work of breathing as PSV is increased.[3,4] The findings of Knebel et al[2] suggest that dyspnea is poorly correlated with work of breathing in ventilator-dependent patients. An alternative—and perhaps more likely—explanation is that the absence of change reflects the extreme difficulty in obtaining accurate and reliable measurements of dyspnea in intubated, critically ill patients. Satisfactory communication with these patients is particularly difficult, and one would wish to have a simultaneous assessment of cognitive function because impairment of the latter may result in misleading ratings of dyspnea. Support for this notion is provided by Keilty et al,[5] who studied ambulatory patients with severe chronic obstructive pulmonary disease (COPD) while they were exercising on a treadmill and receiving PSV by face mask. Their patients reported a systematic reduction in dyspnea with PSV, and the median distance walked was increased by 62%.

Work of Breathing

Measurement of work of breathing is an important objective means of evaluating the efficacy of innovations in ventilator support.[6] Accurate measurement requires close attention to detail; in the past, many important components, such as inspiratory elastic work [including that due to auto-, or intrinsic, positive end-expiratory pressure ($PEEP_i$)] and expiratory work,

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have been omitted. The importance of $PEEP_i$ in this regard is illustrated by data obtained by Coussa et al[7] in patients with COPD receiving controlled mechanical ventilation. They found that work resulting from $PEEP_i$ accounted for about one third of total inspiratory work. Static work was about twofold greater in the patients with COPD than in healthy control subjects, and the difference between the two groups was almost completely explained by $PEEP_i$. Based on these findings, it is evident that a patient may continue to perform a substantial amount of inspiratory work if he or she is being managed using a ventilator mode that does not decrease $PEEP_i$. Thus, if a ventilatory innovation is being introduced, its effect on $PEEP_i$ should be systematically evaluated before its use in clinical practice becomes widespread.

An important limitation of assessment of respiratory work is that the measurements underestimate energy expenditure during isometric or quasi-isometric muscle contractions.[6] To circumvent this problem, many investigators have measured pressure-time product (PTP). This is calculated as the time integral of the difference between pleural pressure (or esophageal pressure, P_{es}) and recoil pressure of the chest wall. The latter is typically measured in a completely relaxed patient receiving a controlled breath with tidal volume and flow settings that are identical to the assisted breath.[6] This can be achieved satisfactorily during assist-control ventilation and IMV, but a problem arises during PSV because lung volume and flow vary from breath to breath in this mode. To overcome this problem, our group[8] developed a modified method of calculating PTP. We first estimated the recoil pressure of the chest wall on a breath-by-breath basis by multiplying chest-wall elastance (previously measured during controlled mechanical ventilation) by lung volume. Then, PTP was calculated as the time integral of the difference between the P_{es} tracing and the recoil pressure of the chest wall. However, an element of uncertainty exists with the measurement of PTP because the rapid decrease in P_{es} before the onset of inspiratory flow may result from inspiratory muscle activity needed to overcome the threshold load imposed by dynamic hyperinflation, *and/or* cessation of expiratory muscle activity. To deal with this issue, we[8] calculated upper and lower bounds of inspiratory PTP, which include the entire possible range of muscular activity (Fig. 1), and also performed analogous calculations to calculate upper and lower bounds of expiratory PTP.

Patients with COPD showed a marked and progressive decrease in inspiratory PTP as PSV was increased from 5 to 20 cm H_2O, but the response among patients was quite variable—with a coefficient of variation of 60-90%.[8] $PEEP_i$ was 4.8 cm H_2O during unassisted breathing and this did not change as PSV was increased. As a result, $PEEP_i$ accounted for 63% of inspiratory PTP at PSV of 20 cm H_2O. This is about twice the value reported by Coussa et al,[7] probably because the patients in the latter study were sedated and paralyzed, where-

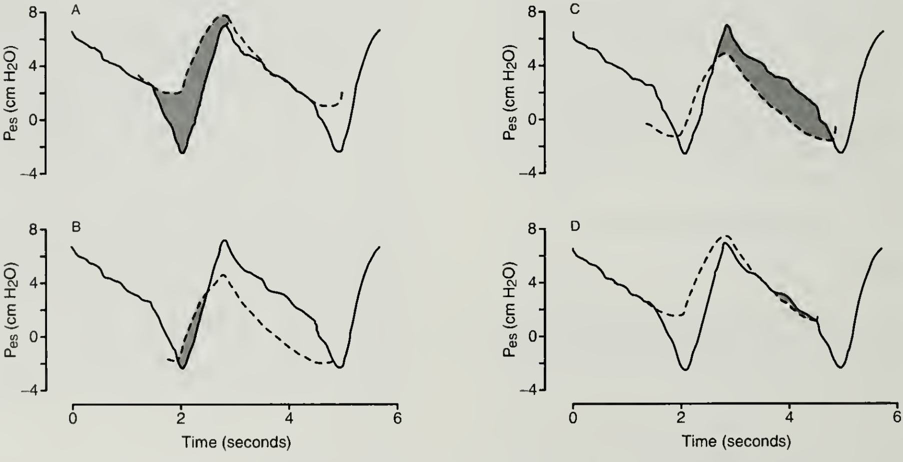

Fig. 1. Tracings of esophageal pressure (P_{es}, ——) and estimated recoil pressure of the chest wall ($P_{es}cw$, ------) in a patient receiving pressure support ventilation. A. Pressure tracings have been superimposed so that $P_{es}cw$ is equal to P_{es} at the onset of the first inspiratory effort, and the integrated difference (hatched area) represents upper-bound inspiratory pressure-time product (PTP_{insp}). B. Pressure tracings have been superimposed so that $P_{es}cw$ is equal to P_{es} at the first moment of transition from expiratory to inspiratory flow, and the integrated difference (hatched area) represents lower-bound PTP_{insp}. C. Pressure tracings have been superimposed so that $P_{es}cw$ is equal to P_{es} at the second moment of transition from expiratory to inspiratory flow, and the integrated difference (hatched area) represents upper-bound expiratory pressure-time product (PTP_{exp}). D. Pressure tracings have been superimposed so that $P_{es}cw$ is equal to P_{es} at the onset of the second inspiratory effort, and the integrated difference (hatched area) represents lower-bound PTP_{exp}. (Reproduced from Reference 8, with permission)

as the patients in our study[8] were triggering the ventilator, and many had evidence of expiratory effort. Measurement of expiratory PTP revealed increased expiratory effort in many patients, especially at higher levels of PSV.[8] Moreover, several patients displayed expiratory muscle activation during the late inflation phase, indicating that the patient was 'fighting' the ventilator (Fig. 2). This was more common in patients who had elevated time constants and who would have required more time for inspiratory flow to fall to the threshold value required for termination of inspiratory assistance by the ventilator (in this case, 25% of peak inspiratory flow). These patients initiated expiratory neuronal activity while the ventilator was still inflating the thorax, resulting in expiratory muscle activity and patient-ventilator asynchrony.

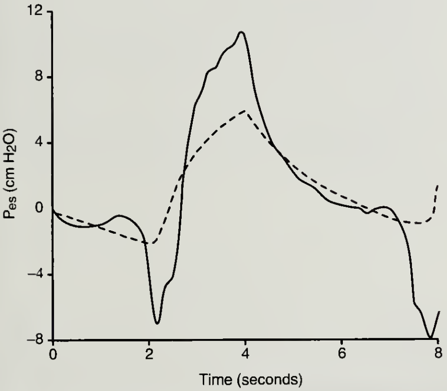

Fig. 2. Tracings of esophageal pressure (P_{es}, ——) and estimated recoil pressure of the chest wall ($P_{es}cw$, ------) in a patient receiving pressure support ventilation of 20 cm H_2O. Pressure tracings have been superimposed so that $P_{es}cw$ is equal to P_{es} at the onset of the rapid fall in P_{es} during late expiration. Times at which the P_{es} tracing are higher than $P_{es}cw$ represents lower-bound expiratory effort. Note the presence of expiratory muscle activation during late inspiration. (Reproduced from Reference 8, with permission)

Pulmonary Gas Exchange

Assessment of the effect of a ventilatory mode on pulmonary gas exchange is usually based on analysis of arterial blood. Assessment is particularly important when a radical change in ventilatory technique, such as high-frequency ventilation, is being introduced. It should be stressed that a satisfactory level of arterial oxygen tension does not guarantee satisfactory tissue oxygenation,[9] and direct measurements of oxygen delivery are preferred.

Muscle Fatigue

Respiratory muscle fatigue is a major concern in ventilator-supported patients, because respiratory muscle rest is the major means of reversing fatigue.[10] However, we still do not have definitive data demonstrating the presence of fatigue in such patients—although indirect evidence, such as an increased tension-time index, suggests its development. Using measurements of tension-time index, Marini et al[11] found that IMV may predispose to the development of muscle fatigue or prevent its reversal. (These findings were made almost 20 years after the introduction of this ventilatory mode to clinical use.) The ideal way to study muscle fatigability is by the construction of a force-frequency curve;[10] however, this is a difficult and painful technique and of doubtful applicability in the critical care setting. A new approach, twitch stimulation of the phrenic nerves (especially using a magnetic stimulator), looks more promising,[12,13] and we await studies with this technique in ventilator-supported patients. One aspect of muscle fatigue that is particularly relevant to evaluation of different ventilatory modes is the long time period required for its reversal—more than 24 hours.[14] It would be interesting to know whether different ventilatory modes can influence the rate and extent of recovery from muscle fatigue.

Issues in Study Design

A final aspect of the use of physiologic end points in the evaluation of ventilatory innovations is the need for careful design of such studies. The control-comparison state needs to be carefully selected; possible options include unassisted breathing, controlled mechanical ventilation, or an accepted mode of assisted ventilation, depending on the question under investigation. Other physiologic variables need to be carefully controlled in such an evaluation. For example, when comparing inverse-ratio ventilation with a conventional mode, the level of $PEEP_i$ needs to be controlled.[15] Also, the timing of the measurements may be important, because some modes may result in progressive recruitment of lung units over time.[16] Finally, the outcomes of the physiologic studies need to be verified by studies of long-term outcome, especially in the case of high-risk or high-cost innovations. Some innovations display apparent advantages when evaluated using intermediate-outcome variables but do not result in improved long-term outcome when subsequently assessed with randomized, controlled clinical trials.[17]

In Summary

It is our view that new ventilatory methods should be withheld from clinical practice until there has been adequate evaluation of their effect on physiologic variables and the link to long-term outcomes has been established. In the past, premature and over-enthusiastic acceptance of ventilatory strategies may have resulted in patient discomfort and even harm, and this can be minimized by a more careful evaluation of the physiologic effects of such innovations before their acceptance into clinical practice.

REFERENCES

1. Tobin MJ. Mechanical ventilation. N Engl J Med 1994;330(15): 1056-1061.
2. Knebel AR, Janson-Bjerklie SL, Malley JD, Wilson AG, Marini JJ. Comparison of breathing comfort during weaning with two ventilatory modes. Am J Respir Crit Care Med 1994;149(1):14-18.
3. Brochard L. Pressure support ventilation. In: Tobin MJ (editor). Principles and practice of mechanical ventilation. New York: McGraw Hill, 1994:239-257.
4. MacIntyre NR. Respiratory function during pressure support ventilation. Chest 1986;89(5):677-683.
5. Keilty SE, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. Thorax 1994; 49:990-994.
6. Tobin MJ, Van de Graaff WB. Monitoring of lung mechanics and work of breathing. In: Tobin MJ (editor). Principles and practice of mechanical ventilation. New York: McGraw-Hill, 1994:967-1003.
7. Coussa ML, Guerin C, Eissa NT, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J. Partitioning of work of breathing in mechanically ventilated COPD patients. J Appl Physiol 1993;75(4):1711-1719.
8. Jubran A, Van de Graaf, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with COPD. Am J Respir Crit Care Med 1995;152(1):129-136.
9. Lutch JS, Murray JF. Continuous positive-pressure ventilation: effects on systemic oxygen-transport and tissue oxygenation. Ann Intern Med 1972;76:(2)193-202.
10. Tobin MJ, Laghi F, Walsh JM. Monitoring of respiratory neuromuscular function. In: Tobin MJ (editor). Principles and practice of mechanical ventilation. New York: McGraw-Hill, 1994:945-966.
11. Marini JJ, Smith TC, Lamb VJ. External work output and force generation during synchronized intermittent mandatory ventilation: effect of machine assistance on breathing effort. Am Rev Respir Dis 1988;138(5):1169-1179.
12. NHLBI Workshop Summary. Respiratory muscle fatigue: report of the respiratory muscle fatigue workshop group. Am Rev Respir Dis 1990;142(2):474-480.
13. Ferguson GT. Use of twitch pressures to assess diaphragmatic function and central drive. J Appl Physiol 1994;77(4):1705-1715.
14. Laghi F, D'Alfonso N, Tobin MJ. Pattern of recovery from diaphragmatic fatigue over 24 hours. J Appl Physiol 1995;79:539-546.
15. Lessard MR, Guerot E, Lorino H, Lemaire F, Brochard L. Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. Anesthesiology 1994;80(5):983-991.
16. Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA. Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 1994;149(6):1550-1556.
17. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 1995;332(6):345-350.

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Clinical Outcome End Points and Assessment of Mechanical Ventilation Innovations

R Phillip Dellinger MD

I. Introduction
II. Considerations in Choosing End Points
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  D. Composites
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Introduction

It is important to observe the effects of mechanical ventilation innovations on physiologic variables. However, our limited understanding of the impact of alteration of a physiologic variable on ultimate clinical outcome indicates the need for assurance that the affected variable is clinically relevant. When the innovation is moderate or high risk, a multicenter trial is typically required because, as seen in Figure 1,[1] large numbers of patients (typically, 300-800 patients) are needed to ascertain differences in clinically relevant variables. The benefit of low-risk innovations may be adequately demonstrated using only physiologic variables in relatively small clinical trials because their use is determined primarily by market influences. It should be remembered, however, that many interventions initially thought to be low risk, such as high oxygen concentrations and high peak inspiratory pressures, are now thought to put the patient at risk for long-term sequelae. Therefore, the utilization of even these lost-cost, low-risk innovations that have been shown to impact only on physiologic variables should be proven to be safe prior to general use.

The use of cost criteria to define rigor of proof of clinical effectiveness is less clear. If moderate-cost or high-cost items are likely to be used regardless of degree of proof of clinical effectiveness, then one could argue for the same requirements expected for moderate- or high-risk innovations. If the market determines use, then less stringent requirements might be required to make the innovation available for use. This is especially true in managed care. In managed care, these innovations are less likely to be used unless they are perceived to impact strongly on clinical outcomes or cost, independent of whether clinically relevant end points were used in research studies. The establishment of credible national committees of experts could publish recommendations for use or non-use of low-risk innovations that have been proven safe and effective based on physiologic variables only.

In this paper, I address the use of clinical-outcome end points in the evaluation of mechanical ventilation innovations for respiratory failure. Although some philosophical and prospective-data guidance exists in the medical literature, very little specifically addresses acute respiratory distress syndrome (ARDS).[2-4] Moreover it is important to realize when discussing these concepts that virtually none of the innovations in me-

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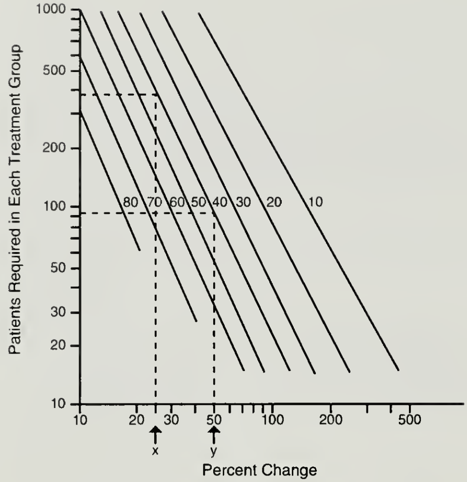

Fig. 1. Nomogram for calculating sample size for a study having a significance of $\alpha = 0.05$ (2-sided) and $\beta = 0.2$ (1-sided). The vertical axis gives sample size for each group; the horizontal axis gives the percent change that can be detected. The diagonal isopleths reflect control group behavior (mortality, for example). "x" and "y" are examples. Example x indicates that 375 patients in each study group are required to detect a 25% reduction in mortality in a population having a baseline 40% mortality (ie, mortality decrease from 40 to 30%). Example y indicates that 94 patients in each study group would be required to find a 50% reduction in mortality in a population having a baseline 40% mortality (ie, mortality decrease from 40 to 20%). As can be seen, the smaller the expected mortality, the greater the sample size required to find the effect. (Adapted from Reference 1, with permission)

chanical ventilation perceived as important over the last 3 decades (eg, PEEP, IMV, pressure support) have been subjected to a carefully controlled outcome study.

Considerations in Choosing End Points

Beneficial effects of innovative mechanical ventilatory therapy are expected to be exerted through improvements in the physiologic status of the patient. Because these physiologic improvements may be counteracted by anticipated or unanticipated deterioration in other physiologic variables (either pulmonary or nonpulmonary) or may indeed be irrelevant to the patient's long-term hospital course, physiologic end points are often classified as 'soft.' However, improvements in such physiologic end points are critical in determining which of many innovative interventions should be entered into clinical testing for proof of 'harder' end points.

Morbidities that have been proven or accepted to correlate with mortality, quality of life, or cost savings (so called 'hard end points') should be considered as appropriate, clinically relevant end points for moderate- or high-risk mechanical ventilation innovations.

Mortality as an End Point

A predetermined degree of change in mortality is the ultimate end point that is generally accepted by all, if it is proven to have statistical significance. All-cause mortality is most appropriate, as opposed to pulmonary-related mortality, due to the problems with blinding. Because innovations in mechanical ventilation are difficult or impossible to blind, significant chance exists for introducing observer bias in judging cause of death (pulmonary versus nonpulmonary) in that circumstance. Even if the study can be blinded, it may be difficult to precisely judge cause of death in many patients, thereby, introducing the possibility of sample imbalance.[5]

A mortality end point has important sample size considerations. In general, adequate sample size for a mortality-end-point study involving a mechanical ventilation innovation depends upon the relationship of the innovation's effect on lung function to ultimate mortality. The weaker this relationship, the larger the sample size required (Fig. 1).[1]

In some diseases, such as status asthmaticus, the primary morbidity and the mortality of the disease are directly correlated with the degree of impairment in lung function. In such diseases, it is reasonable to assume that improvements in lung function tightly correlate with improvements in mortality. This mortality improvement should be demonstrable in a clinical trial of moderate size if the anticipated mortality is high enough among the targeted patient population. Unfortunately, most patients with life-threatening respiratory failure also have other organ failure that can be fatal independent of the lung disease.[6] For example, in ARDS, pulmonary-related mortality is thought to be 15-20%. That is not to say that mechanical ventilation issues might not have positive or negative impact on nonpulmonary causes of death (for example, those that can be related to prolonged mechanical ventilation). Thus, a mechanical ventilation innovation that is truly beneficial in improving lung function may not statistically reduce mortality in a condition (such as ARDS) unless large numbers of patients are enrolled because of its inability to affect the predominantly nonpulmonary deaths.

Therefore, the proof of clinical utility by evaluation of mortality in patient populations in which the lung is one of several involved organ systems is problematic. Thus, there is the probability of not showing a statistically significant benefit on mortality when one does exist (ie, a β error) due to inadequate power of the study (failing to enroll a sufficiently large number of patients). If there is a physiologic benefit that decreases mortality in patients who were destined to live or die based on lung function, it might only be proven in two circumstances when patients with disease frequently characterized by multiple organ dysfunction are studied: (1) enrolling large numbers of patients to avoid a β error; and (2) limiting the patient enrollment to only those patients without other organ system dysfunction.

Both of these approaches make the study excessively long and/or involve many more investigative sites. In either case, there is an important disincentive to public or private funding of such a trial due to excessive cost at a time when funding for clinical research, over all, is tenuous.[7] In addition, if a large number of sites are used, the expected lower enrollment at each site may increase the chance of sample imbalance due to differences in types of patients and the approach to treatment for respiratory failure among sites. If enrollment is restricted to a subsample of the disease process likely to die from pulmonary causes, an additional problem may be the lack of ability to generalize benefit once it is proven.

Alternatives to Mortality as an End Point

Morbidity

Situations in which a morbidity end point may be used as a substitute for mortality end point include: (1) the morbidity end point is proven or generally accepted to be linked to mortality; (2) the morbidity end point is proven or generally accepted to be linked to cost savings; and (3) the morbidity end point is proven or generally accepted to be linked to quality of life or decreased pain or suffering. The mechanisms for offering convincing proof for the latter two morbidity end points are controversial and currently in a developmental stage.[8-10] In this paper, I address the potential for use of morbidity end points proven or generally accepted to be linked to mortality in ARDS. Examples of morbidity end points that are generally accepted to correlate with mortality and/or cost savings in mechanical ventilation of respiratory failure are days on mechanical ventilation, days in ICU, and days in hospital. A problem with each of these variables is that when death is hastened by progression of the underlying illness, days on mechanical ventilation, days in ICU, and days in hospital also decease even in the absence of treatment benefit. A potential solution for this problem with mechanical ventilation is to choose the end point of "days alive off mechanical ventilator support." An additional advantage of this variable is that it is tied to mortality in that patients must survive their respiratory failure to have days alive off mechanical ventilator support. Therefore, this is somewhat of a combined morbidity-mortality end point. Other morbidity end points, such as barotrauma or hospital-acquired pneumonia, would be presumed to correlate with mortality. It is interesting that gut decontamination in critically ill ICU patients has been demonstrated to decrease hospital-acquired pneumonia without a statistically significant effect on mortality, even when large groups of patients are studied.[11]

Surrogates

It is possible to consider physiologic variables or other soft end points as surrogate end points, if these physiologic variables are linked to harder, more accepted morbidity or mortality end points.[12,13] This requires validation from large databases of the patient population in which the mechanical ventilation innovation will be studied.[14] This is accomplished using logistic regression techniques of statistical modeling.[15] For example, if one were to study the effect of a new intervention in ARDS patients using a physiologic variable that had been shown through analyses of large databases of ARDS patients to correlate with mortality, that variable could be considered a surrogate end point for mortality. Others would argue that surrogate end points can only be used provided some similar intervention in ARDS has been shown to decrease that surrogate end point in direct correlation with a decrease in mortality. Examples of single physiologic variables that might be considered for surrogate end points include reduction of inspiratory plateau pressure and reduction in F_{IO_2}. The use of these surrogate end points would be based primarily on animal data with some, less optimally controlled human experience.[16-18] The use of an index such as P_{aO_2}/F_{IO_2} would be another option in ARDS, although the impact of oxygenation defect on survival appears to be less strongly linked than other nonpulmonary factors.[19] Single physiologic variables as primary end points may create study design problems. This can be demonstrated with the designations of an end point in a clinical trial of inhaled nitric oxide in ARDS. In that circumstance, the hypothesis would be that if significant improvement in P_{aO_2} occurred with inhaled nitric oxide, the response of the healthcare provider would be to decrease F_{IO_2}, airway pressure, or PEEP. Without rigid treatment guidelines, it is difficult to predict, however, which ventilator setting would be adjusted for a particular patient and, therefore, choosing among a change in inspiratory plateau pressure, a change in the F_{IO_2}, or a change in PEEP as the primary end point would be problematic.

Indices as Surrogates

Indices as surrogate end points have recently been advocated in innovative therapy of sepsis. Again, as for single physiologic surrogate end points, validation is required. An example is a risk-prediction index of death developed by Knaus and colleagues.[20] This index was derived using historical pieces of patient information, physiologic and laboratory variables, and special hospital characteristics of the patient. This index was retrospectively fitted to a large database of patients with sepsis and was then validated by field testing in a smaller group of patients. It was then used in the first, large phase-III randomized trial of interleukin-1 receptor antagonist, IL-1ra, in patients with severe sepsis, to stratify the patients in the analysis.[21] The results suggested that IL-1ra benefited patients with mortality predictions of ≥ 24%. Because this was a post hoc analysis, a second large trial was required to justify use of the risk-prediction index as the primary efficacy variable. Unfortunately, the second trial failed to show benefit in that group (personal communication, Charles J Fisher MD, 1994). What the impact of this will be on future utility of similarly derived indices is not clear. In either of the circumstances listed for choosing surrogate end points, a beneficial effect on the surrogate variable ideally should be associated with clear assurance of no toxic or secondary negative effect. This is best done by linking the statistically significant surrogate effect with a positive trend in mortality or a mortality-linked morbidity variable (such as days alive off mechanical ventilatory support).

Composites

It is possible to do a statistical test in which multiple variables are analyzed with one statistical test (composite end point).[22,23] O'Brien's generalized least squares and the approximate likelihood ratio are two such statistics. These statistical analyses may be capable of proving a treatment effect when the treatment is anticipated to impact on multiple variables in a beneficial way because it is not known which variable will be primarily affected. These variables may include some combination of physiologic and morbidity variables as well as the potential to include mortality. If there is a difference favoring the innovative treatment in any variable added to this statistical analysis, the chance to show statistical significance is improved. Likewise, the chance of showing statistical significance is decreased with any added variable that favors neither treatment group or favors the non-innovative therapy. This might lead to a demonstration of significant statistical difference by allowing selection of, perhaps, three physiologic variables that are expected to improve with the innovative therapy when it is difficult to pick a single variable that is likely to reflect the primary beneficial alteration. In addition, the possibility exists of including an accepted morbidity or mortality variable to the composite end point in circumstances where a difference in favor of the innovative therapy was likely to occur, but small numbers of patients could prevent statistical proof using that single variable.

Need for End-Point Selection

Prospective Definition of Variables

Regardless of what the variable is for which a statistical significant effect of the innovative mechanical ventilation treatment is claimed, that variable should be prospectively identified and have been the single test by which the success of the mechanical ventilation innovation was to be judged. This is true for a composite end point, a physiologic end point tied to a trend in mortality, and a surrogate end point. Prospective identification of multiple end points to be tested requires selection of a procedure to control the error rate existing with use of a p value of ≤ 0.05. A p value that reflects efficacy after adjustment for the numbers and types of analyses performed should be used for statistical significance (statistical penalties).[24,25] This will prevent an α error (claiming a benefit when no benefit exists).

Control of Covariants

Treatment of respiratory failure may vary considerably among sites in a multicenter study. This is true regardless of the cause of respiratory failure, (eg, status asthmaticus, COPD, neuromuscular failure, or ARDS). It is ideal to have a common ventilator management strategy for respiratory failure among the sites involved so that the mechanical ventilation innovation becomes the single variable most likely to vary among the treatment groups. For example, if a mechanical ventilation innovation is being studied in ARDS, agreement among investigators in the use of PEEP (eg, optimal PEEP based on compliance or inflection point), limitation of inspiratory plateau pressure (eg, to allow some degree of permissive hypercapnia), and priorities for decreasing PEEP versus decreasing mean airway pressure versus decreasing F_{IO_2} in response to improvement of oxygenation is desirable. This treatment strategy may be as sophisticated as a computerized algorithm or as simple as a list of basic principles to be used as guidelines.[26,27] An additional potential benefit of protocol management or treatment guidelines is improving the chance of establishing the validity of a selected physiologic surrogate variable.

In Conclusion

It must also be remembered that the adequate and fair evaluation of an innovative mechanical ventilation therapy with any chosen end point depends on study design issues such as power of the study, randomization, blinding, choice of specific statistical tests, and time over which treatment is evaluated.[28,29] These and other issues are covered elsewhere in this conference.[30]

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REFERENCES

1. Young MJ, Bresnitz EA, Strom BL. Sample size nomograms for interpreting negative clinical studies. Ann Intern Med 1983;99(2): 248-251.
2. Ritschel WA. Standards of clinical investigations in the USA. Meth Find Exp Clin Pharmacol 1993;15(4):207-215.
3. Terrin ML. Efficient use of endpoints in clinical trials: a clinical perspective. Stat Med 1990;9(1-2):155-160.

4. Schooley RT, Strongin W, Hawley P. Design of clinical trials—end points. J Acquir Immune Defic Syndr 1990;3(Suppl 2):572-574.
5. Dellinger RP. Clinical trials in adult respiratory distress syndrome. New Horiz 1993;1(4):584-592.
6. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985;132(3):485-489.
7. Hurd SS, Lenfant CJM. Pulmonary research: what topics? what costs (editorial)? Am Rev Respir Dis 1987;135(3):521-522.
8. Butler RN. Quality of life: can it be an endpoint? how can it be measured? Am J Clin Nutr 1992;55(6, Suppl):1267S-1270S.
9. Aaronson NK. Quality of life assessment in clinical trials: methodologic issues. Controlled Clin Trials 1989;10(4, Suppl):195S-208S.
10. Chang RWS, Beale R, Smithies M, Bihari D. A preliminary cost-performance evaluation of HA-1A (cenotoxin) with an addendum on its demise. Clinical Intensive Care 1993;4:208-216.
11. Vandenbroucke-Grauls CM, Vandenbroucke JP. Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. Lancet 1991;338 (8771):859-862.
12. Schatzkin A, Freedman LS, Schiffman MH, Dawsey SM. Validation of intermediate end points in cancer research. J Natl Cancer Inst 1990;82(22):1746-1752.
13. Boissel JP, Collet JP, Moleur P, Haugh M. Surrogate endpoints: a basis for a rational approach. Eur J Clin Pharmacol 1992;43(3): 235-244.
14. Tüysüz B, Ozlu I, Aji DV, Erginel A. Prognostic factors in meningococcal disease and a new scoring system. Acta Pediatr 1993;82(12):1053-1056.
15. Lemeshow S, Le Gall JR. Modeling the severity of illness of ICU patients. A systems update. JAMA 1994;272(13):1049-1055.
16. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985;132(4):880-884.
17. Dreyfuss D, Saumon G. Lung inflation: physiologic and anatomic alterations leading to pulmonary edema. Zapol WM, Lemaire F, editors. Adult respiratory distress syndrome. New York: Marcel Dekker, 1991:433-449.
18. Hickling KG, Henderson SJ. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia. Intensive Care Med 1990;16(6):372-377.
19. Knaus WA, Sun X, Hakim RB, Wagner DP. Evaluation of definitions for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;150(2):311-317.
20. Knaus WA, Harrell FE, Fisher Jr CJ, Wagner DP, Opal SM, Sadoff JC, Draper EA, et al. The clinical evaluation of new drugs for sepsis. A prospective study design based on survival analysis. JAMA 1993;270(10):1233-1241.
21. Fisher Jr CJ, Dhainaut JFA, Opal SM, Pribble JP, Balk RA, Slotman GJ, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome: results from a randomized, double-blind, placebo-controlled trial. Phase III. JAMA 1994;271(23):1836-1843.
22. Tang DI, Geller NL, Pocock SA. On the design and analysis of randomized clinical trials with multiple endpoints. Biometrics 1993;49 (1):23-30.
23. O'Brien PC. Procedures for comparing samples with multiple endpoints. Biometrics 1994;40:1079-1087.
24. Friedman LM, Furberg, CD, DeMets DL. Fundamentals of clinical trials, 2nd ed. St Louis: Mosby Yearbook 1985:256.
25. Woolson RF. Statistical methods for the analysis of biodmedical data. New York: John Wiley & Sons, 1987:327-337.
26. Morris AH. Randomized clinical trials (editorial). ASAIO Trans 1991;37(2):41-42.
27. Sittig DF, Gardner RM, Morris AH, Wallace CJ. Clinical evaluation of computer-based respiratory care algorithms. Int J Clin Monit Comput 1990;7(3):177-185.
28. Cook DJ, Jaeschke R, Guyatt GH, Journal Club of the Hamilton Regional Care Group. Critical appraisal of therapeutic interventions in the intensive care unit: human monoclonal antibody treatment in sepsis. J Intensive Care Med 1992;7:275-282.
29. Donahoe M, Rogers RM. An anecdote is an anecdote is an anecdote … but a clinical trial is data (letter). Am J Respir Crit Care Med 1994;149(2, Part):293-294.
30. Rubenfeld GD. Study design: statistical and methodologic considerations. Respir Care 1995;40(9):980-986.

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Study Design: Statistical and Methodologic Considerations

Gordon D Rubenfeld MD

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Introduction

In the 50 years since the landmark trial of streptomycin in pulmonary tuberculosis, the randomized control clinical trial (RCT) has emerged as the gold standard for evaluating medical therapies.[1] Because of definitive RCTs we no longer freeze gastric ulcers or administer steroids for septic shock.[2,3] Experiments, such as these, are capable of establishing a causal link between a therapy and its effect. However, causal inference is one that investigators make cautiously when data come from observational and nonexperimental study designs. Often, the phrase "is associated with" is used in place of "causes" because there are many plausible alternative explanations in addition to the hypothesized causal one. Randomization, when combined with proper blinding and outcome ascertainment, is a powerful research tool precisely because it reduces the chances that observed associations are not causal. In this paper, I introduce the reader to the concepts of chance, confounding, and bias and explain how RCTs deal with their effects.

The high quality information from RCTs, like that obtained from gold-standard diagnostic tests in clinical practice, is purchased at a high price. These studies are expensive to perform and often require individual patients and physicians to abrogate their personal choices regarding the best therapy. Given these limitations, an RCT cannot be performed to answer every clinical question that arises. Inevitably, decisions about implementing new or continuing to use old medical therapies will come from a synthesis of information from a variety of sources. The type and quality of evidence required prior to widespread medical use will need to be matched to the expense, risk, and uncertainty of the therapy under consideration. Whereas a large RCT with mortality as an end point is necessary to demonstrate the superiority of partial liquid ventilation, it is intellectual overkill to expect this level of evidence prior to using a new ventilator humidifier. To meet the competing demands of evidence-based practice of medicine, cost containment, and prompt provision of effective therapies, study designs must be tailored to the research question. The methodologic and design characteristics of the RCT and its role in determining the efficacy of medical therapies are the foci of the paper.

Sources of Error in Clinical Trials

If human beings were identical, like specially bred laboratory mice or mechanical test lungs, and if their environment, diet, and medical care could be completely specified, then randomization would rarely be necessary. Perfect human trials could be conducted because the study and control groups would be identical in every way except one—the experimental treatment. It is unfortunate, from a research standpoint, that

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human beings and their diseases are influenced by innumerable factors, both known and unknown, that make it impossible to construct study groups that are identical in every way. Because study and control groups will necessarily differ in some ways, researchers need a method to distinguish between the differences that are due to the treatment and those due to other causes of observed differences. Randomization and blinding, by eliminating bias and reducing confounding to chance, provide researchers with a powerful tool in their search for causal relationships.[4,5]

Bias

The hallmark of scientific research is its reproducibility. Two scientists studying a drug in similar patients should find a similar effect within the bounds of chance. Experiments are designed and analyzed in an effort to provide an unbiased estimate of this effect. In fact, this is exactly what unbiased means to a statistician. An unbiased coin is one that yields results completely according to chance—heads are as likely as tails on every toss. An experiment that provides an unbiased estimate of treatment effect is one that is just as likely to undershoot the true effect as it is to exaggerate it. Biased study designs consistently yield results that deviate in one direction, much as a biased scale consistently over- or underestimates weight. If the bias is known, the direction, although not always the magnitude, can be determined.[6]

Studies that compare a new treatment to historical controls are biased toward finding the new treatment beneficial.[7,8] Researchers who allocate patients as they see fit may choose to place patients with more favorable prognoses in the study group. This design biases the study towards finding a favorable effect of the treatment. Randomization is usually effective at eliminating these biases that are introduced at the time the control and study groups are formed. However, randomization alone does not eliminate biases that creep in at other points after the formation of the study groups.

A few examples of these post-randomization biases should suffice. Studies that compare only treatment responders, compliant patients, or those who actually complete therapy to a randomized control group are biased toward finding an effect. The most conservative method for controlling this bias is the 'intention-to-treat' approach in which everyone who is randomized to treatment is included in the analysis as having received it, regardless of whether they actually did receive it or respond to it. This intention-to-treat method has been criticized as overly conservative, and techniques are being developed to analyze data from patients who receive care different from that specified in their original assignment.[9]

Investigators may, unconsciously, assign borderline cases as successes or failures based on knowledge of the treatment received. Blinding investigators is the best insurance that all patients in both arms are regarded similarly with respect to their care and to the ascertainment of end points. However, in studies that evaluate surgical procedures and many types of medical devices, blinding is difficult. This limitation has complicated the critical evaluation of mechanical ventilator weaning strategies. A clinician with full knowledge of the treatment received is often in the position of deciding when to extubate the patient. Subtly, and quite unconsciously, keeping control patients on the ventilator a few hours longer and aggressively extubating those in the experimental group is enough to introduce bias. When it is not possible to blind the practicing clinician to the assignment, it is important to develop rigid guidelines for ancillary medical decisions and strict criteria for counting end points and complications. Those who evaluate these end points should not be the same individuals who provide the unblinded care.

Confounding

Differences in mortality may not be due to the treatment but to other differences between the patients. If control patients are older and sicker, this may account for the lower mortality in the treatment group. When the effect of the treatment on mortality (in this case, the new ventilator) is mixed with other effects (eg, severity of illness or age) the two are said to be *confounded*. For this to occur, the potential confounder must be associated with both the treatment and outcome. This means that an imbalance between the two groups must be present, and this imbalance must also be associated with the outcome.[10] Differences in eye color or astrologic sign, even large differences, would not confound the relationship between ventilator mode and mortality. In epidemiologic studies in which patients are not randomized, potential confounders must be identified and controlled in the analysis of the data. Even after this analysis, residual or uncontrolled confounding is always a potential explanation for associations found in epidemiologic studies.

A common misperception is that randomization eliminates confounding by creating identical study and control groups. Frequently, it does create groups that are roughly similar on a wide range of measured variables. However, the real purpose of the procedure is to create groups that *do* differ from each other but do so in a specific way, that is, they differ randomly.[11,12] Confounding variables, those that are strongly related to the outcome, are also distributed randomly, and the effect of confounding is reduced to the effect of chance imbalances in the study groups. We are left with the mathematical problem of estimating the probability that chance differences in the groups account for observed differences in outcome. This is exactly the question that tests of statistical significance were designed to answer.

Chance

Table 1 contains data from a hypothetical trial showing a 50% reduction in mortality ($p = 0.005$). Few numbers are more frequently misinterpreted and overutilized than the nominal p-value result from a statistical test. The double negative, "probability of rejecting the null hypothesis when the null hypothesis is true," although a correct definition of p, no doubt contributes to the confusion surrounding this hallowed formulation. The p value simply reflects the probability of obtaining the same results (mortality reduction = 50%) or more extreme ones (mortality reduction of > 50%) if, in fact, the treatment has no effect, and the difference in the result is due to chance imbalances among groups of patients.

Table 1. Hypothetical Trial Data Showing a Treatment Effect = 50% Reduction in Mortality—95% Confidence Interval (0.25, 0.96), $p = 0.005$

Condition	Treatment	Control
Dead	30	15
Alive	20	35
Mortality (%)	60	30

Consider a clinical trial with 100 patients who are randomly assigned to 2 groups but in which no therapy is provided, and both groups get the same placebo injection. Now suppose that you have been funded to repeat this 'null' experiment 1,000 times. Of course, in the majority of trials you will see nearly identical mortality in each group. Some of the randomizations will lead to an imbalance in the assignment of patients who will die. How often might this lead to the data in Table 1? The p value (0.005) tells you that only 5 of these 1,000 'null' experiments will show differences as extreme or more extreme as those in Table 1—mortality reduction ≥ 50%. By making chance an unlikely explanation of these data, we have also made confounding an unlikely explanation.

Distinguishing "statistical significance" (a low p value) from clinical importance is essential for those who wish to apply the results of trials. Three factors determine the p value: the magnitude of the difference between groups, the sample size, and the variability in the outcome measure. Large differences in precisely measured variables in many subjects lead to very small p values. However, a p value of any given significance (say, less than 0.05) can be generated from very small differences if they are measured in enough subjects. Large and clinically important effects may be missed (that is, fail to meet a specific p-value criterion), if the outcome variable is measured inaccurately or if the sample size is small. It is as incorrect to accept all studies as clinically significant because they achieve a low p value as it is to reject as clinically unimportant all studies that fail to reach some arbitrary level of statistical significance.

Clinical trials should have a reasonable chance of concluding that the effect of interest is statistically significant. Small negative studies contribute little information because they cannot exclude important treatment effects.[13] The probability of concluding that a specified treatment effect is statistically significant when, in fact, such efficacy exists is called power. A study's power is determined by the magnitude of the treatment effect, the threshold of statistical significance set by the investigators, and the variability in the outcome measure. Using estimates for these values, researchers can calculate the number of patients they must recruit for a given study.

Unfortunately, the results of this calculation are often discouraging. If investigators are only interested in treatments with large effects, then relatively small sample sizes will suffice. To have a 90% chance of finding results identical to those obtained in Table 1 (a reduction in mortality from 60% to 30%) at the $p = 0.05$ would require only 60 patients in each arm of the study. However, effect sizes this large are unusual in medicine and particularly unlikely in critically ill patients where mortality is likely to be multifactorial. Clinicians may feel that much smaller mortality reductions are clinically important. Enormous sample sizes are necessary to reliably conclude that small differences are statistically significant. To detect a reduction in mortality from 60% to 55% (an 8% reduction as opposed to the 50% reduction in the previous example) with the same power and statistical significance requires more than 2,000 patients in each arm of the study.

A variety of techniques can be used to maximize statistical power, other than recruiting more patients. Limiting the study to patients who are likely to benefit the most will present a large effect size. Investigators may decide that a p value of 0.10 is persuasive enough for their purposes. By accepting a higher p value, they are accepting a higher risk of adopting an ineffective therapy, but that risk must be balanced against the benefits of a smaller sample size. There are advantages to be gained by substituting a continuous variable, like blood pressure or P_{O_2}, for categorical variables, such as mortality. Detecting an 8% reduction in average duration of mechanical ventilation, from 12 to 11 days, only requires several hundred patients in each study arm.

If random noise (variation) in the outcome variable can be reduced, for example, by measuring physiologic variables precisely or by providing care according to a protocol, sizable reductions in sample size can be obtained. More than 300 patients are needed for the duration-of-mechanical-ventilation study just described, if the standard deviation (SD, variability) in the outcome is 4 days. If instituting a protocol reduces SD to 2 days, the sample size requirement drops to around 100 patients. Paired study designs are also powerful tools for controlling variability. By taking measurements before and after the randomized intervention, each patient's baseline data serves as a ruler for measuring improvement. The investigator then compares, for example, the *change* in P_{O_2}, for the treatment and control groups.

Models of illness severity like APACHE (Acute Physiology and Chronic Health Evaluation) or MPM (Mortality Prediction Model) have been proposed as methods to reduce variation in clinical trials.[14,15] By mathematically controlling for variations in illness severity, advocates contend that small treatment effects will emerge as statistically significant in studies where they would not otherwise. In fact, there are potential advantages of such a model-based approach.[16] Unfortunately, because even good prediction models account for a relatively small amount of variation, the gains in precision are modest and are achieved at the expense of a simple representation of the results.[17] The goal is not to control confounding but to control the 'noise' or random variability. If investigators choose to adjust for prognostic variables, it is imperative that the variables be selected *prior to* analyzing the data. By creatively dredging through a variety of predictors it is possible, with this technique, to create a statistically significant treatment effect where none, in fact, exists.[18]

Factorial study designs improve power by allowing a group of patients to contribute information on more than one treatment.[19] If the effects of two therapies can be expected to act independently of each other, for example, a ventilatory mode and an anti-inflammatory sepsis drug, a 2 × 2 factorial design can be implemented. Here one fourth of the patients are randomized to a control arm, one fourth receive the new ventilatory mode, one fourth the pharmacologic intervention, and one fourth receive both interventions. The control group's data and the dual treatment group's data can be counted separately in the analysis of the ventilator mode *and* the drug treatment. This effectively increases the sample size for a given number of patients.

Covariate Imbalance & the p Value

The p value tells the reader the probability that an experiment would return a given set of data if the treatment is ineffective and the observed differences are due simply to chance imbalances in confounding variables. Let us assume we do not have the information that is usually provided in the traditional 'Table 1' of an RCT report—ie, the distribution of the confounding variables among groups. Considering the 50%-mortality-reduction example, we do not know whether the treatment group was sicker or older than the controls. What are the chances of observing the 50% mortality reduction if it were due only to chance imbalances in age or severity of illness? Exactly 5 in a thousand—the p value. Now, what if the average age of the treatment group is half that of the control group? What are the chances of observing this magnitude of mortality reduction if the differences are only due to chance imbalances? The reason we randomized in the first place is so that we can answer this question, and the answer is the same—exactly 5 in a thousand.

What are we to make of the trial that fails to create similar study and control groups? Just as a well-shuffled deck of cards occasionally deals straight flushes, randomized studies occasionally yield imbalanced patient groups. We sometimes say that these trials suffer from inadequate or failed randomization. Unless there is evidence that the investigators committed fraud, the concept is better expressed as 'unlucky' randomization. We know that the treatment effect, the p value, and the confidence interval obtained from an RCT are unbiased regardless of the chance imbalances. This means that if we repeat the exact experiment over and over, 95% of the 95% confidence intervals will contain the true effect, and the study findings will only differ by chance. Individual researchers find little solace in the notion that repeating a study over and over will lead to reliable results when they got an unlucky deal of the randomization cards. There are three ways to deal with the post-study anxiety generated by chance imbalances in confounding variables.

Showing in the traditional 'Table 1' that treatment and control groups are similar with regard to measured variables does not prove that unmeasured important variables were distributed in a balanced fashion. As long as randomization and blinding were performed correctly, the effect of these imbalances on the estimate of treatment effect will be adequately expressed in the p value and confidence interval. Because the 'Table 1' comparisons don't really change the interpretation of the treatment effect, p value, or confidence interval, some commentators feel this information is superfluous.[10,20] So, the first method for dealing with imbalances is to compulsively and blindly randomize subjects and forego looking for differences among groups in baseline characteristics. However, scrutinizing such tables has become fairly ingrained in reviewers and, despite the arguments of some statisticians, papers without this information are unlikely to be widely accepted.

The second method for handling imbalances is to prevent them. A variety of randomization strategies allocate patients within groups defined by the investigator. For example, young and old patients can be randomized separately to ensure that age is similarly distributed between treatment and control groups. This method entails more work for the investigators but ensures balanced allocation for certain variables. Of course, this method cannot guarantee balanced unmeasured variables—the p value is still necessary to evaluate their effect. Stratified randomization guarantees that 'Table 1,' at least for the specified variables, will contain no surprises. Finally, investigators can control covariate balance in the analysis. It is interesting to note that even in trials with very unlucky randomization and gross covariate imbalance, the adjusted analyses rarely change the study findings.[17,21]

Limitations of Randomized Clinical Trials

There is little disagreement that RCTs provide the best evidence for drawing conclusions about the efficacy of a therapy. However, randomized controlled trials raise ethical questions, are expensive, address a specific question, and may not reflect the effectiveness of a therapy in the 'real world' of the practice of medicine. Given the large sample sizes needed to detect small effects, prolonged observation times for chronic-disease projects, and the large administrative burdens of studies, the costs of RCTs can be enormous. One particularly exhaustive and complex trial, the Multiple Risk Factor Intervention Trial (MRFIT), cost more than $116,000,000.[22] Funding for trials of new treatments should come from the industries that stand to profit from them, but many practices in clinical medicine have evolved without sufficient empirical evidence. Financial pressures may induce health-care payers such as the federal government and managed care entities to invest in studies to evaluate current practice. Whereas it is difficult to weigh the costs of RCTs against the costs of proceeding with a therapy of unknown efficacy, it is clear that multimillion-dollar studies cannot be performed for every clinical question in every conceivable population.

Although human trials have a sometimes sordid ethical history, current practice is closely watched by institutional review boards.[23] Clinical equipoise is the ethical principle that justifies randomization.[24] When serious disagreement as to the appropriateness of a therapy exists in the professional community at large, even if individual physicians in individual cases have strong opinions, then an RCT is ethically justifiable. The AIDS epidemic and patient-advocacy movements have raised difficult questions about patients' rights—particularly the rights of patients with terminal illnesses to have access to any care that might benefit them.[25] Time spent planning, coordinating, and publishing RCTs often leads to a discrepancy between promising treatments that appear in the laboratory and the clinical evidence to support their use. There will always be some new therapy, device, or diagnostic test that threatens to make recently completed RCTs obsolete even before the data are published. Society will need to weigh the importance of firm knowledge about medical treatment efficacy against the competing needs of the desperately ill for access to any care that might help them.

Proponents of RCTs are frequently faced with a dilemma. This dilemma has been described as the efficacy-effectiveness, fastidious-pragmatic, or validity-generalizability issue. Broadly speaking, the question is whether a trial should be designed to answer a single clean question in a narrow patient population in a few high-quality centers or whether it should be opened up to include a broad range of patients and practitioners. The former design generates an efficacy trial and answers the narrow question, In the best of hands *can* this therapy work in a specified patient population? If the results of an efficacy trial are positive, critics will be concerned that generalization to other centers or patients is unjustified. Effectiveness or "large simple" trials seek to enroll a broad range of patients at many institutions.[26] Proponents argue that this design more closely reflects the sort of practice that will occur if the therapy is adopted. When negative, there is always the concern that efficacy in a subgroup was obscured or that some of the providers were unskilled. Like most dilemmas, there is no ready solution to the efficacy-effectiveness design debate. There is general agreement that when efficacy trials with sufficient statistical power have been negative, large effectiveness trials are difficult to justify. Neither design is preferred—they provide complementary information.

There are two main alternatives to doing an RCT. The first is not truly an alternative method. Meta-analysis quantitatively synthesizes the results of many RCTs into a standardized estimate of the underlying treatment effect.[27] Many small negative trials that lack statistical power can, collectively, contribute information to a statistically significant estimate of effect. The use of many trials, each with different patient populations and settings, may replicate the type of information available from a "large simple" randomized trial.[28] Criticisms of this analytic technique center on the 'apples-and-oranges' problem. It may not make sense to mix studies with various formulations of the therapy and diverse end points. If studies are selected for inclusion in the meta-analysis in a biased fashion then the results of the meta-analysis will be biased. Despite its problems, meta-analysis may provide enough information to avoid the expense of a large confirmatory trial, when the evidence of many smaller trials can be combined.

The other important alternative, a study design that has been dubbed the 'outcome study,' has been added to the researcher's armamentarium. It is important that readers understand that the outcome study and the burgeoning field of outcomes research is, in reality, an old and venerable study design that has been modified slightly to serve a new purpose. Traditionally, in an epidemiologic cohort study, a group of subjects is assembled and followed for a period of time. Some of the patients, presumably by chance, will come in contact with tobacco, ethanol, asbestos, or a number of other exposures of interest. Subjects are assessed for the development of disease, and relative risks for the exposures are calculated. Confounding is a major methodologic impediment that is usually surmounted with models that mathematically control for multiple variables and present an unconfounded estimate of the exposure's effect.[29] Despite these sophisticated techniques, bias and residual confounding remain alternative explanations for associations noted in cohort studies.

The outcome study is identical to the cohort study except the exposure is not to tobacco or electromagnetic radiation but to a medical therapy, such as coronary angioplasty or tympanostomy-tube insertion. Just as cohort studies try to establish a causal link between the exposure and the disease, outcome studies attempt to establish a causal link between the medical therapy and some improvement in a clinically important outcome. This outcome may be mortality or days alive off the ventilator, but, more recently the focus of the outcomes movement has shifted to health-related quality of life.

Confounding, reduced to a measurable chance phenomenon in RCTs, is a big problem in outcome studies of medical therapy. The same multivariate models used in epidemiologic cohort studies are used to control for severity of illness and other factors that distinguish those who were selected for a therapy from those who were not. However, when clinicians are permitted to choose who receives a treatment, even among patients with nearly identical objective parameters, the selected patients seem to do better irrespective of the treatment's efficacy. This indication bias may drive outcome studies toward concluding that ineffective treatments are effective.[30] Unless the subtle factors that clinicians use to make their selections can be measured and controlled, this is a difficult bias to eliminate.

Outcomes research has many advantages over clinical trials. Data about patients, the treatments they receive, and their outcomes are collected in the course of routine care for administrative and quality-improvement purposes. The data reflect care as it is actually being provided outside of the academic walls. There are some encouraging data about the reliability of information obtained from these nonrandomized studies. Results of RCTs can be closely simulated from clinical databases suggesting that, at least in some fields, indication bias is not always an uncontrollable source of error.[31] Several studies with parallel RCTs and observational arms have found similar results in both.[32,33] Outcome studies may be particularly helpful in evaluating the effectiveness of standard treatments that were never evaluated with RCTs in which evidence of inefficacy or harm would raise serious questions. Outcomes research cannot substitute for RCTs in the evaluation of new therapies whose efficacy has never been demonstrated.

The Cost/Risk Matrix & Clinical Trials

The Consensus Statement presents a matrix of study end points: engineering, physiology, and clinical-outcomes assessment. Study designs need to be tailored to the specific research question and end points under consideration. The RCT may not be indicated or feasible for every question. The evidence necessary to adopt an innovation needs to be proportional to the cost, risk, and uncertainty surrounding the therapy. Minor engineering improvements, particularly those that lead to less-expensive treatments, may only require bench testing. In this setting, randomization is not necessary because test equipment can, for the most part, be expected to perform in a fashion similar to test animals. Randomization is important in evaluating the ability of new ventilator equipment to meet physiologic efficacy criteria. The paired study design offers the ability to improve power by measuring physiologic variables before and after the experimental intervention. Blinding is often omitted in these trials, but an argument can be made for its use. Potential bias can even be introduced by reading gauges and choosing when to perform blood-gas assessments. Consequently, the person evaluating the end point or making assessment decisions should not know which group the patient is in—caregivers should be blinded to the assignment.

Before expensive and risky medical therapies are endorsed for widespread use they should be evaluated by an RCT using important clinical end points. It is imperative that these studies contain a plan for evaluating costs.[34] When this is not done as part of the study, the economic impact of the therapy will eventually need to be modeled on incomplete data. Because cost-effectiveness analyses will play a growing role in the decisions to adopt treatments, high-quality economic data are essential. The use of non-randomized epidemiologic studies, or outcomes research, to evaluate therapy is still evolving. This technique is poorly suited to the evaluation of emerging technologies. Though methodologically imperfect, outcomes research provides an ongoing critical evaluation of real-world medical effectiveness that is not available by any other means.

In Conclusion

Randomized controlled clinical trials are extremely powerful research tools. The ability to virtually eliminate bias and confounding greatly enhances our ability to draw causal inferences about medical therapy. Synthesizing the evidence to select appropriate medical treatments places society in a position similar to the practicing clinician's diagnostic dilemma. Clinicians frequently are forced to make difficult decisions with incomplete data. The best test cannot always be obtained in time to make a crucial treatment choice. When we are faced with uncertainty, a more expensive or dangerous confirmatory diagnostic test can almost always be done. Clinicians must balance the additional information from additional testing against the benefits of urgent treatment based on available data. It would be unreasonable to perform bronchoscopy on every patient with a pulmonary infiltrate or a magnetic resonance scan on every patient with back pain. Similarly, every question about treatment effectiveness cannot be subjected to the gold-standard workup—a randomized controlled trial. The ideal setting for an RCT is one where the potential costs to society are great, where the potential harm to patients is significant, and where great uncertainty exists.

REFERENCES

1. Council MR. Streptomycin treatment of pulmonary tuberculosis. BMJ 1948;2:769.
2. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317(11):653-658.
3. Ruffin JM, Grizzle JE, Hightower NC, McHardy G, Shull H, Kirsner JB. A co-operative double-blind evaluation of gastric "freezing" in the treatment of duodenal ulcer. N Engl J Med 1969;281(1):16-19.
4. Meinert CL, Tonascia S. Clinical trials: design, conduct, and analysis. New York: Oxford University Press; 1986.
5. Hulley SB, Cummings SR. Designing clinical research: an epidemiologic approach. Baltimore: Williams & Wilkins; 1988.
6. Sackett DL. Bias in analytic research. J Chronic Dis 1979;32(1-2): 51-63.
7. Sacks H, Chalmers TC, Smith H Jr. Randomized versus historical controls for clinical trials. Am J Med 1982;72(2):233-240.

8. Sacks HS, Chalmers TC, Smith H Jr. Sensitivity and specificity of clinical trials. Randomized v historical controls. Arch Intern Med 1983;143(4):753-755.
9. Sheiner LB, Rubin DB. Intention-to-treat analysis and the goals of clinical trials. Clin Pharmacol Ther 1995;57(1):6-15.
10. Senn SJ. Covariate imbalance and random allocation in clinical trials. Stat Med 1989;8(4):467-475.
11. Brennan P, Croft P. Interpreting the results of observational research: chance is not such a fine thing. BMJ 1994;309(6956):727-730.
12. Greenland S. Randomization, statistics, and causal inference. Epidemiology. 1990;1(6):421-429.
13. Freiman JA, Chalmers TC, Smith H Jr, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. Survey of 71 "negative" trials. N Engl J Med 1978;299(13):690-694.
14. Le Gall JR, Lemeshow S, Leleu G, Klar J, Hilliard J, Rue M, et al. Customized probability models for early severe sepsis in adult intensive care patients. Intensive Care Unit Scoring Group. JAMA 1995; 273(8):644-650.
15. Knaus WA, Harrell FE, Fisher CJ Jr, Wagner DP, Opal SM, Draper EA, et al. The clinical evaluation of new drugs for sepsis. A prospective study design based on survival analysis. JAMA 1993;270(10): 1233-1241.
16. Robinson LD, Jewell NP. Some surprising results about covariate adjustment in logistic regression models. International Statistical Review. 1991;59:227-240.
17. Shapiro SH, Louis TA. Clinical trials: issues and approaches. New York: M Dekker, 1983.
18. Enas GG, Enas NH, Spradlin CT, Wilson MG, Wiltse CG. Baseline comparability in clinical trials: prevention of "poststudy anxiety." Drug Information Journal. 1990;24:541-548.
19. Byar DP, Piantadosi S. Factorial designs for randomized clinical trials. Cancer Treat Rep 1985;69(10):1055-1063.
20. Begg CB. Suspended judgment. Significance tests of covariate imbalance in clinical trials. Control Clin Trials 1990;11(4):223-225.
21. Aspirin-Myocardial Infarction Study Research Group. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980;243(7):661-669.
22. Feinstein AR. Current problems and future challenges in randomized clinical trials. Circulation 1984;70(5):767-774.
23. Beecher HK. Ethics and clinical research. N Engl J Med 1966;274 (24):1354-1360.
24. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317(3):141-145.
25. Wachter RM. AIDs, activism, and the politics of health. N Engl J Med. 1992;326(2):128-133.
26. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. J Clin Epidemiol 1995;48(1): 23-40.
27. Dickersin K, Berlin JA. Meta-analysis: state-of-the-science. Epidemiol Rev 1992;14:154-176.
28. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327(4):248-254.
29. Robins JM, Greenland S. The role of model selection in causal inference from nonexperimental data. Am J Epidemiol 1986;123(3): 392-402.
30. Holmberg L, Steineck G. Indication for treatment can introduce bias in observational studies of surgical treatment (editorial). Eur J Surg Oncol 1993;19(3):223-225.
31. Hlatky MA, Califf RM, Harrell FE Jr, Lee KL, Mark DB, Pryor DB. Comparison of predictions based on observational data with the results of randomized controlled clinical trials of coronary artery bypass surgery. J Am Coll Cardiol 1988;11(2):237-245.
32. Hammermeister KE, DeRouen TA, Murray JA, Dodge HT. Effect of aortocoronary saphenous vein bypass grafting on death and sudden death. Comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. Am J Cardiol 1977;39(6):925-934.
33. Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. N Engl J Med 1984;310(11):674-683.
34. Adams ME, McCall NT, Gray DT, Orza MJ, Chalmers TC. Economic analysis in randomized control trials. Med Care 1992;30(3): 231-243.

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Resources for Assessing Innovations in Mechanical Ventilatory Support: The Missing Link

Thomas D East PhD

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Introduction

A study from the Office of the Assistant Secretary of Health, Department of Health Education and Welfare (now the Department of Health and Human Services) suggests that for three different major diseases 85% of medicine has never been scientifically proven to produce more benefit than harm.[1] Economic pressures and health-care reform have forced the health-care industry as well as respiratory care to carefully question what aspects of patient care are ineffective and can be eliminated.[2-7] Respiratory care has seen an explosion of new technology in the last 20 years. Respiratory care is by its nature highly technologic and is susceptible to the allure of new mechanical ventilation technology that promises creative solutions to difficult clinical problems. With the exception of high-frequency ventilators,[8] virtually all of the innovations in mechanical ventilation introduced in the last 20 years have not required proof of efficacy prior to introduction in the commercial clinical arena. This has left us with a legacy of unproven mechanical ventilation techniques and styles.[9-13] Unfortunately, we know relatively little about which innovations are truly efficacious and at what cost.

Although the concept of using only therapies that can be proven to provide more benefit than harm seems obvious, implementing that concept is not a simple or inexpensive task. Assessment of new technology has traditionally fallen into 3 categories: engineering testing, clinical trials with intermediate outcome measures, and outcome studies. Figure 1 illustrates typical costs for each type of technology evaluation.

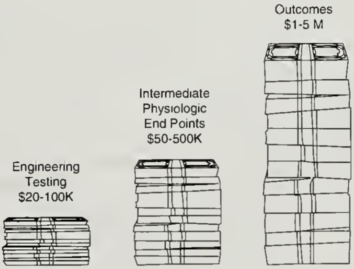

Fig. 1. The approximate costs of three different types of technology assessment for mechanical ventilation—engineering testing, clinical trials with intermediate physiologic outcome measures, and clinical trials using outcome measures such as mortality.

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Engineering testing is the easiest, the least expensive, and the most common form of technology assessment in mechanical ventilation. Engineering testing establishes that a new technology functions as designed, measures its likelihood for failure, and documents its function following failure conditions. Engineering testing is essential to demonstrating feasibility of a new technology; however, it does not prove clinical efficacy.

Mechanical ventilation is used to care for patients with a wide variety of respiratory problems from simple to complex. Therefore, no one measure clearly indicates the overall 'benefit' of mechanical ventilation. Intermediate outcome measures, such as P_{aO_2}, P_{aCO_2}, pH, $P_{plateau}$, and P_{peak} are attractive because they are easy to measure frequently and thus allow relatively small studies of moderate cost to have sufficient statistical power to test the null hypothesis. However, a new technology that improves P_{aO_2} but decreases survival is not likely to garner wholehearted clinical acceptance. Ultimate outcome measures, such as changes in morbidity and mortality, are clearly defensible clinical outcomes; however, a clinical trial designed to show a 12% difference in a baseline mortality of 50% would require over 400 patients. If a 5% difference in mortality is considered clinically important and worth the risk and cost of the new technology, a study of over 1,000 patients would be required to test the null hypothesis with adequate statistical power. Such a large multicenter clinical trial would cost in excess of $3 million.

The cost of large clinical trials can be borne by the pharmaceutical industry, based on the shear volume of sales, but the profit margin does not allow ventilator manufacturers to spend millions of dollars on clinical trials for every innovation. Figure 2 illustrates the fundamental dilemma; asking that all technology be proven clinically efficacious reduces the number of ineffective products reaching the market; however, it also stifles the introduction of many that are effective.[14] How can we as a respiratory care community decide which technologies are valuable and which can be discarded? What resources are available for technology assessment? These questions loom large as health-care reform descends upon us.

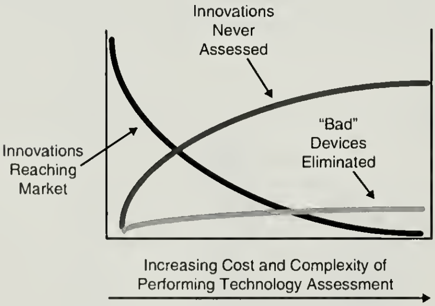

Fig. 2. The tradeoffs inherent in increasing complexity and cost of technology assessment: As the cost and complexity increase, the number of ineffective technologies identified increases; however, the number of innovations assessed drops markedly as industry can no longer afford to bring them to market.

Financial Resources Currently Available

A MEDLINE search for information regarding resources for technology assessment revealed no references for the field of respiratory care. Financial resources for conducting assessment of innovations in mechanical ventilation may be available from the federal government, industry, professional societies, consumer groups, insurers, hospitals, health-care corporations, and foundations.

Federal Government

There are two government agencies specifically charged with the task of technology assessment:

The Office of Technology Assessment (OTA)
600 Pennsylvania Ave SE
Washington DC 20510-8025
202-224-9241

The Office of Health Technology Assessment (OHTA)
Agency for Health Care Policy and Research (AHCPR)
6000 Executive Boulevard, Suite 309
Rockville MD 20852
301-594-4023

The OTA performs only the technology assessments that are assigned to them by committees of the U.S. Congress. These assessments are reviews of existing literature and surveys of experts in the field. No new testing or clinical trials are conducted. They have done no assessments related to respiratory care.

The OHTA performs technology assessments for federally funded reimbursement programs.[15] These federal reimbursement programs include the Health Care Financing Administration (HCFA) and the Office of Civilian Health and Medical Programs of the Uniformed Services (OCHAMPUS). The OHTA has developed a scoring system (Table 1)[16] for prioritizing technologies as candidates for assessment. OHTA assessments are reviews of existing literature and surveys of experts in the field. No new testing or clinical trials are conducted. They have done no assessments related to mechanical ventilation; however, in 1991 they performed an assessment of intermittent positive-pressure breathing.[17]

The Public Health Service (PHS) supports technology assessment through its normal investigator-initiated grants (R01) and its Small Business Innovative Research (SBIR) programs.

Applications are made through the standard PHS grant-application procedures (Form PHS 398). Typical agencies within the PHS that support work related to respiratory care are the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI), and the AHCPR. Information can be obtained from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Bethesda MD 20892, Telephone: 301-496-7441.

Table 1. Office of Health Technologies Assessment Scoring System for Prioritizing Technologies for Assessment.*

Score Component	Weight
The potential for a technology to improve health outcomes or to affect costs	4.8
The morbidity and mortality associated with the health condition	3.5
Variations in current practice	2.8
The economic burden posed by the prevention, diagnosis, treatment, and clinical management of the health condition	2.7
Aggregate cost of the use of the technology	2.7
The prevalence of the health condition	2.6
The ability of the assessment to inform ethical, social or legal issues	1.8

*Each component is given a score ranging from 1-5. This score is then multiplied by the weighting factor, and the results are summed.[16]

In the past, NIH and its NHLBI have been focused on basic science research and relatively uninterested in technology assessment and clinical outcomes research. This focus may be shifting as pressures mount to provide outcomes research documenting the benefits of technology. In 1994, NHLBI established a network of 10 clinical centers to conduct over the next 7 years randomized clinical trials of new technology for treatment of patients with ARDS. This includes mechanical ventilation. The first trial conducted will investigate the efficacy of small tidal volumes with permissive hypercapnia. Investigator-initiated R01 grant applications to NIH can be submitted through the regular PHS application process. R01 grants are judged on scientific merit, with NIH policy relevance a secondary concern. SBIR grants are a potential source of NIH funds for technology assessment for small businesses that are developing an innovative technology. Phase-1 SBIR grants are typically 6-month to 1-year grants and are focused on taking an innovative concept to the point of proven feasibility. Phase-1 trials are limited to $75,000 in direct costs. Phase-2 SBIR grants are designed to provide resources to take a new technology through trials designed to demonstrate efficacy. These funds can be used to conduct larger clinical trials. Phase-2 trials are limited to $250,000 in direct costs. During 1993, 905 grants were awarded (654 Phase 1, 251 Phase 2) for a total of $121 million.[18] Two projects were somewhat related to respiratory care: (1) Long Duration Open-Circuit Respirator—Phase 1 and (2) Lighter, Compact Respirators for Toxic Vapor Protection—Phase 2.

Within the AHCPR, the Division of Quality and Technology Assessment in the Center for General Health Services Extramural Research is primarily responsible for assessment of innovation. Their efforts are divided between Patient Outcome Research Teams (PORTs) and investigator-initiated R01 grants. The PORTs focus on identifying the most effective management for a particular health condition. PORTs are multidisciplinary, multisite, large scale, and long term. Each PORT conducts a literature review and synthesis including meta-analysis. They also analyze variation in medical practice from existing database information. The PORT must disseminate its findings and evaluate the effects of this dissemination. The AHCPR currently funds 14 PORTs. None of these are in the field of respiratory care. Investigator-initiated R01 grant applications can be submitted through the regular PHS application process. R01 grants are judged on scientific merit, with AHCPR policy relevance a secondary concern. In general, the AHCPR receives grants focused on outcomes research. Research directed at medical issues that impact a large population and consume large health-care resources are more desirable.

The National Science Foundation (NSF, 4201 Wilson Blvd, Arlington VA 22230, 703-306-1234) is a possible source of funding for innovation assessment. Investigator-initiated R01-type grants can be submitted using the standard NSF Grant Application Process. The grant proposals are judged on scientific and technical merit, with NSF policy relevance a secondary concern. Our experience suggests that their interest is in innovative scientific methods rather than the assessment of existing technologies.

Industry

Industry provides a large portion of the resources currently applied to assessment of innovation in mechanical ventilation and performs a majority of the engineering testing as part of their research and development of new products. This testing and small clinical trials using intermediate outcome measures are the foundation of their FDA submissions. Marketing and/or sales departments also support assessment of technology if they believe that the results of the study will be useful as a marketing tool. Industrial support of randomized controlled clinical trials (RCTs) or other outcomes research is rare. The notable exception to this has been the assessment of high-frequency ventilation, and this was due to the FDA requirement that these devices undergo 'pre-market' approval as a new life-support device. Industrial technology may be assessed internally or contracted. Companies, such as Citech (Plymouth Meeting PA) provide engineering testing, literature reviews, and assistance with FDA submissions. Academia has conducted a large amount of industry-sponsored engineering testing and is the sole source for the clinical trials.

My experience has been that manufacturing companies are rarely interested in supporting a large definitive clinical trial to prove efficacy or effectiveness of new technologies; they want to do the minimum necessary for FDA approval and clinical acceptance. A definitive trial carries high risks for the company. What if the result is that the new technology, for which they have invested millions, is shown to be ineffective? From a business perspective, it may be better to not know the answers to such questions.

Industry typically initiates contact with outside contractors; however, they do entertain unsolicited proposals for technology assessment. These proposals should be short and to the point, and should be more similar to a business prospectus than a PHS grant proposal.

Consumer Groups

Consumer groups, such as the University Hospitals Consortium (Evanston IL), are putting resources into assessment of technology to improve purchasing decisions for the entire consumer group. This research may be largely review of literature and expert opinion; however, it can also include engineering testing and small clinical trials. ECRI (Plymouth Meeting PA) is a nonprofit research agency that has conducted a large number of technology assessments for consumer groups and for insurers and health-care organizations. They provide engineering testing as well as a technology information service that summarizes technology assessment on a variety of medical devices.

Insurers

Third-party payers of any kind have a vested interest in reducing the cost of health care. As was mentioned, HCFA puts resources into technology assessment through the OHTA. Other insurance companies also do technology assessment. Most of the assessment is done by literature review and expert opinion. It may include engineering testing. It is rare that insurers pay for a clinical trial of any kind.

Hospitals & Health-Care Organizations

As capitated reimbursement becomes the rule, hospitals and health-care organizations are carefully scrutinizing all of the technology with the hopes of being able to eliminate it. It appears to be exceedingly difficult to convince health-care-organization managers to purchase innovative technology in the absence of a compelling cost/benefit argument. Continuous quality improvement (CQI) and continuous process improvement (CPI) dissect health-care processes and attempt to improve the quality of care and reduce costs.[19-23] An integral part of these activities is technology assessment. Hospitals and health-care organizations are investing large resources into these efforts in the hopes of identifying effective health-care processes and technology. Assessment includes engineering testing and clinical trials with intermediate-cost outcomes (ie, length of stay). Outcome studies are rare; however, they have been performed and their number will probably continue to grow. The key to these resources is that they will be poured into processes that are viewed by the organization as high cost, high volume, and high waste. Unfortunately, unless a health-

Table 2. A List of Foundations* that Have Supported Research on Respiratory-Health Topics.

American Respiratory Care Foundation (ARCF)
11030 Ables Lane
Dallas TX 75229-4593
2-3 projects/year—$30,000 total

The Whitaker Foundation
901 15th St NW, Suite 1000
Washington DC 20005
4 projects/year—$360,000 total

The Chatlos Foundation
PO Box 915048
Longwood FL 32791-5048

The Coca-Cola Foundation
One Coca-Cola Plaza NW
Atlanta GA 30313-3009

The Continental Corporation
180 Maiden Ln, #12-B
New York NY 10038

Ira W DeCamp Foundation
c/o Mudge, Rose, Guthrie, Alexander, & Ferdon
630 Fifth Ave, Suite 1650
New York NY 10011

Edouard Foundation
c/o Phillips Nizer, et al
31 West 52nd St, 15th Floor
New York NY 10019

The Francis Families Foundation
800 West 47th St, Suite 604
Kansas City MO 64112

Charles A Frueauff Foundation
307 East Seventh Ave
Tallahassee FL 32303

Hasbro Children's Foundation
32 West 23rd St
New York NY 10010

The Hearst Foundation
888 Seventh Ave, 45th Floor
New York NY 10106-0057

Ambrose Monell Foundation
c/o Fulton, Duncombe, & Rowe
30 Rockefeller Plaza, Room 3217
New York NY 10112

Pew Charitable Trusts
One Commerce Square
2005 Market St, Suite 1700
Philadelphia PA 19103-7017

Rockefeller Foundation
420 Fifth Ave
New York NY 10018-2702

Thrasher Research Foundation
50 East North Temple St, 7th Floor
Salt Lake City UT 84150

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*Reproduced with permission from a search done using Reference 23.

care organization is large, it may be difficult or impossible to conduct studies large enough to provide unambiguous answers to the research questions.

Foundations

Table 2 contains a list of foundations that might provide grants for respiratory care technology assessment.[24] As you can see, there is no strong history of foundations' funding assessment of mechanical ventilation; however, future funding is not impossible. Foundations tend to be more interested in projects that appear to have the likelihood of having a large impact on humanity. Assessing mechanical ventilator technology may not appeal to all foundations and may be viewed as too narrow a topic, with little impact on large populations of patients. However, most foundations do accept investigator-initiated grant proposals. Each foundation has different requirements for submission.

Current Status of Funding for Technology Assessment

Table 3 contains examples of typical mechanical ventilation technology assessment studies and my own experience with the potential for funding from various sources. The information in Table 3 indicates a general lack of interest in funding outcomes research on mechanical ventilation technology. At present, industry provides the largest fraction of the funding for such assessments. Unfortunately, this is far below the amount of funding needed to assess much of the technology in mechanical ventilation. If as a society we consider that somewhere between 30 and 85% of health-care costs are spent on technology that is ineffective,[1] it seems reasonable to invest a portion (less than 30-85%) of the national health-care budget to determine which technologies are most effective, resulting in an overall net savings. Unfortunately, if large-scale, prospective, randomized trials focused on ultimate outcomes are required for all technologies, the costs will rapidly consume any anticipated savings. The current costs for taking a new drug through technology assessment—up to $194 million and 7-10 years[14]—is an example of this. This process prevents harmful technologies from reaching the market; but, as shown in Figure 2 it also prevents industry from even considering many potentially useful technologies. This concept is supported by evidence from research-and-development budgets for drug companies that increased by only 4% (to 13.1 billion) in 1994 compared to 13.5% in previous years.[14] Medtronic (Minneapolis MN), a medical device manufacturer, now spends $75 million to develop a new product[25]—three times what it cost them in 1990. Few medical devices companies can support this kind of cost. Nearly 80% of device makers have less than $20 million in revenues each year.[25]

An OTA report on the status of federal programs for assessment of medical technology[26] concluded that AHCPR's programs have created a fertile ground for outcomes research focused on clinical outcome measures using new research applications of large databases. OTA concludes that "the federal effort has been largely unsuccessful with its initial charge: evaluating the comparative effectiveness of alternative treatments." PORTS were described as not being a "particularly useful tool in providing valid, believable answers about comparative effectiveness."

Table 3. Examples of Different Technology Assessment Studies and the Funding That Would Probably Be Available for This Study Today.

Technology Assessment Study	Funding Availability			
	NIH	AHCPR	Industry	Foundations
Randomized controlled trial (RCT) comparing pressure-control, inverse-ratio ventilation (PCIRV) and volume-controlled ventilation (VCV) 400 Patients $1,000,000 over 3 years	No, no mechanistic or basic science questions	No, not a big enough problem	No, does not sell ventilators, not required by FDA	No, too big a project
RCT comparing pressures and gas exchange between PCIRV and VCV 100 Patients $200,000 over 2 years	No, who cares about gas exchange?	No, not a large enough problem	No, doesn't promote sales, not required by FDA	No, too big a project
Cross-over study comparing pressures and gas exchange between PCIRV and VCV 20 Patients $20,000 over 1 year	No, poorly designed study	No, not a problem, bad study	OK if it promotes sales or if needed for FDA approval	Maybe, not exciting idea
Take the new ventilator on loan for 6 months; try new modes on some patients; publish a paper on results $5,000	No, poorly designed study	No, not a problem, bad study	OK, it promotes sales & marketing	No, not science

Unfortunately, as health-care organizations and insurers are being 'squeezed' for dollars, refusal to pay for any clinical procedures viewed as experimental is a growing trend.[25] In the summer of 1994, Health and Human Services investigators subpoenaed records from 132 research centers, including Mount Sinai (New York NY) to see whether government programs were fraudulently billed for investigational cardiac devices in the past 7 years. A recent article[25] describes the dilemma of the patients wanting new technology to improve outcomes and a system in which no one is willing to pay to develop and assess this new technology. They draw the analogy of a "boiler with a broken relief valve—pressure is building, and an explosion seems imminent." Mount Sinai has responded by canceling all device trials. An executive of Medtronic states that "This is one of the most important issues in the research world today."[25]

Future Directions

It is clear that we have a problem. Mechanical ventilation is a field that is filled with unproven technology, and few resources are available for technology assessment. What are the options open to us? If there are no new resources available, the obvious solution seems to be to reduce the cost of technology assessment. This is being done now by prioritizing technologies and focusing only on technologies that are in widespread use and may be ineffective.[16] This does reduce the cost of assessment; however, it also reduces the potential savings and leaves a large pool of unproven technology.

OTA in their analysis of this field made the following recommendations:[26]

- Conduct more, high-quality meta-analyses and other systematic overviews of existing studies, to make the best use of past efforts at clinical evaluation.

OTA would implement this by increasing funding for systematic reviews, by requiring new studies to prove that their hypothesis has not already been answered by previous work, and by maintaining a database at the National Library of Medicine containing information on published controlled clinical trials.

- Conduct more and more efficient clinical trials that yield valid comparative information on existing technologies, with results directly useful to patient and clinician decision making; and make valid, well-designed comparative studies an intrinsic part of ordinary practice in every setting.

They envision this being accomplished by close collaboration between AHCPR and NIH, establishment of a database of ongoing clinical trials (both federally funded and private), and the investment in a nationwide, community-based research infrastructure that could be used for conducting large, community-based clinical trials.

- Encourage greater comparative evaluation of newly introduced technologies by offering incentives to manufacturers, by encouraging or requiring payers to link payment for new technologies only if it is part of a clinical trial for assessment of effectiveness, and by expanding the role of government in sponsoring technology assessment.

An alternative perspective is that we as a society are paying for technology assessment without realizing it. Today's reality is that every year, more than 1 million people are supported with mechanical ventilators. Each of these patients is a miniature clinical trial with $n = 1$. The clinician chooses the ventilator, mode, and management carefully to provide optimal care. This means that a huge amount of resources are spent each year optimizing management of mechanical ventilation. If even $100/patient is spent on this task, a total of $100 million is spent each year. The net result, however, is that we still have no data of sufficient power to fully determine what is truly effective. However, those 1 million patients on ventilators could, with the same outlay of resources, serve as the samples for 100 large clinical trials ($n = 10{,}000$), and 100 important technology-assessment questions could be answered each year!

The key to this is collaboration among members of the respiratory care community. The two main requirements are: (1) Standardized data collection to allow data from many sites to be easily pooled. (2) Standardized management of mechanical ventilation to assure that new technology is used the same way by all clinicians. A nationwide community-based respiratory care research infrastructure is exactly what OTA is suggesting (See the second recommendation, above).

Technology assessment has been and always will be a central part of respiratory care practice. In the future, routine respiratory care will include following a study protocol for a new device or drug; however, the goals will remain similar: delivering high quality respiratory care, charting information in a standard manner, and following patient-driven protocols for the management of mechanical ventilation. Only the content of the research protocols would change from study to study. A collaborative, nationwide, respiratory care research network may be the only viable solution to the resource dilemma posed by assessment of new mechanical ventilation technology.

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REFERENCES

1. Williamson JW, Goldschmidt PG, Jillson IA. Medical practice information demonstration project. Final report. Baltimore MD: Office of the Assistant Secretary of Health, DHEW, 1979.
2. Abramowitz KS. The future of health care delivery in America. New York: Sanford C Bernstein & Company, 1988.
3. Hughes EFX. The challenges facing American medicine, the search for a new equilibrium and its implications for physician executives. In: New leadership in health care management, the physician executive. American Academy of Medical Directors, 1988.
4. Lundberg GD. National health care reform. An aura of inevitability is upon us (editorial). JAMA 1991;265(19):2566-2567.
5. Mayer D. U.S. likes its care but not the cost. Healthweek News 1991;5(5):2-30.
6. Mulley AG, Eagle KA. What is inappropriate care? JAMA 1988; 260(4):540-541.
7. Nutter DO, Helms CM, Whitcomb ME, Weston DW. Restructuring health care in the United States. JAMA 1991;265:2516-2520.
8. Froese AB, Bryan AC. High frequency ventilation. Am Rev Respir Dis 1987;135(6):1363-1374.
9. Perel A. Newer ventilation modes—temptations and pitfalls. Crit Care Med 1987;15(7):707-709.
10. Marini JJ. Mechanical ventilation and newer ventilatory techniques. In: Bone RC, editor. Pulmonary and critical care medicine (Volume 2). St Louis: Mosby Year Book, 1993:1-23.
11. Quan SF. A ghost from the past: low tidal volume mechanical ventilation revisited. Chest 1990;97(2):261-262.
12. Räsänen J. Mechanical ventilatory support-time for appraisal. Int & Crit Care Dig 1991;10(1):3-5.
13. Snyder JV, Carroll GC, Schuster DP, Culpepper J, Klain M. Mechanical ventilation: physiology and application. Curr Probl Surg 1984;21(3):1-87.
14. ECRI. Must assessment stunt innovation? Health Technol Assessment News 1994;January-February:1-5.
15. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. Process for technology assessments and recommendations for coverage. Federal Register 1993;58(231):63988.
16. Agency for Health-Care Policy and Research. Proposed methodology for establishing priorities for health care technology assessments. Federal Register 1994;59(79):19725.
17. Agency for Health-Care Policy and Research. Intermittent positive pressure breathing (IPPB) therapy. AHCPR Health Technology Assessment Reports 1991;1. Washington DC: U.S. Department of Health and Human Services, 1991.
18. Small Business Innovation Research (SBIR) Phase-I and Phase-II Projects Abstract Book Fiscal Year 1993. Bethesda MD: U.S. Government Printing Office, 1994;300-997/13588.
19. Eddy DM. Variations in physician practice: the role of uncertainty. Health Aff 1984;3(27):74-89.
20. Eddy DM, Billings J. The quality of medical evidence: implications for quality of care. Health Aff 1988;7(1):19-32.
21. Eddy DM. Clinical decision making. JAMA 1990;263:1265-1275.
22. James BC. Quality management for health care delivery. Chicago: American Hospital Association—Hospital Research and Educational Trust, 1989.
23. James BC. TQM in clinical medicine. Frontiers of Health Services Management 1991;7(4):44-48.
24. Search of foundations that support research in pulmonary and respiratory care. DIALOG INFORMATION SERVICES File 27: Foundation Grants Index, ©1994 The Foundation Center, 79 Fifth Ave, New York, New York 1003-3076, 212-620-4230.
25. Scott L. Hospitals try to devise solutions to device debate. Modern Healthcare 1995;February 20:34-38.
26. Office of Technology Assessment. OTA report summary—identifying health technologies that work: searching for evidence. Washington DC: U.S. Government Printing Office, 1994:1-8.

FACE TO FACE WITH CHANGE

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Respiratory Infections: A Scientific Basis for Management, edited by MS Niederman MD, GA Sarosi MD, and J Glassroth MD, with 77 contributors. Hardcover, 657 pages, illustrated. Philadelphia: WB Saunders. 1994. $134.95.

Drs Niederman, Sarosi, and Glassroth have assembled a state-of-the-art review of respiratory infections. This book addresses the current resurgence of interest in respiratory infections and meets the needs of both clinicians and scientists. Certain types of infection are becoming increasingly more common in the 1990s, eg, nosocomial pneumonia. At the same time that the complexities of respiratory infections are increasing, the technologies for diagnosis, treatment and prevention are expanding. Presented in a new format, this text fulfills a need for current information about respiratory infections.

The authors focus on a clinical approach to specific populations at-risk for respiratory infection. This systematic and clinical approach, rather than being organism-directed, encourages health-care providers to consider the clinical and epidemiologic picture of the patient before searching for a specific microbial cause for the lung infection. The authors have exposed a firm scientific foundation for such an approach; and, I believe that the authors have accomplished this very well. As a result, the book provides relevant information for understanding the pathogenesis of pneumonia and other respiratory infections in an easy-to-read and comprehensible text.

Respiratory Infections: A Scientific Basis for Management is divided into 6 sections. The book starts with a scientific review of infection pathogenesis, specifically the pathogenesis of pneumonia, and provides the principles upon which clinical assessment and diagnostic and therapeutic strategies are based.

The next section, Clinical Approach to Upper and Lower Respiratory Tract Infections in Specific Populations, provides the clinical core because it is devoted to respiratory infections as they occur in specific risk groups. A review of the signs, symptoms, and likely pathogens for lung infection in each group is also presented in this section. The objectives are to direct the clinician to early consultation with other professionals at the initial evaluation of a patient and to focus on the diagnosis and therapy appropriate for each patient. The next section reviews the specific features of individual respiratory pathogens that cause pneumonia.

The last three sections contain practical reviews of methods for handling laboratory specimens, using therapeutic antimicrobial agents, and preventing respiratory infections. In all, 51 chapters, by 77 contributing authors, have been expertly edited so that little repetition of information can be detected.

This text is concise and organized so that the reader can easily cull and understand the information. Tables are used to summarize information in each chapter. Figures, chest radiographs. schematic drawings, and electron microscope images illustrate the chapters very well. References are listed at the end of each chapter. The index at the end of the text is thorough.

Respiratory Infections: A Scientific Basis for Management is written for physicians. However, this reference could be used by all health-care providers involved in the care of patients with respiratory infections. I would recommend that therapist-level respiratory therapy programs obtain a copy for their faculty and students.

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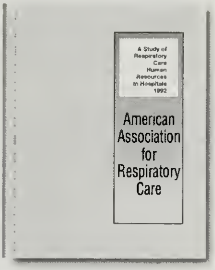
The AARC Human Resources Survey: A Study of Respiratory Care Human Resources in Hospitals


A Study of Respiratory Care Human Resources in Hospitals 1992
American Association for Respiratory Care

Covers a wide range of human resource issues, including compensation, numbers of full-time equivalents, job vacancy rates, education, credentialing, and licensure. Even includes information on age, sex, and years of experience. Includes comprehensive summary, position profiles, salaries, education, experience, credentials, and regional demographics. Vacancies are inventoried. 68 pages, 66 tables.

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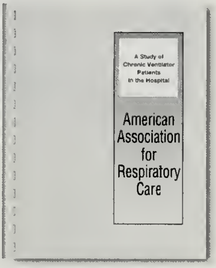
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Chronic ventilator-dependent patients are costing American hospitals more than $9 million per day according to this Gallup study conducted for the AARC. This important study provides information on patients who depend on life-support systems; why, how, and where they are being treated; and the cost of treatment. 47 pages, 9 tables, 12 figures.

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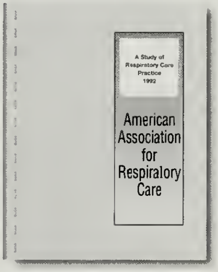
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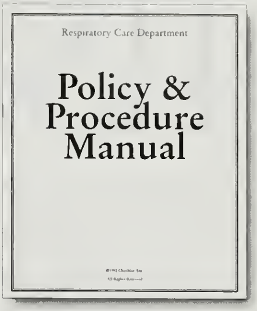

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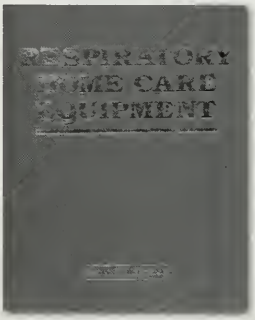

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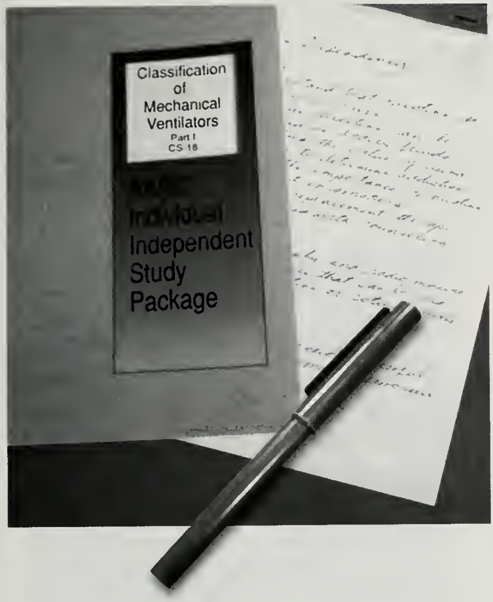

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Pulmonary Function Assessment I: Basic Screening Studies

Understand simple spirometry results, the definition of obstructive and restrictive pulmonary disorders, and the basic pathology involved in each. Covers the four reasons for simple spirometry tests, the common parameters of lung function, and the results that are indicative of obstructive and restrictive pulmonary disorders.

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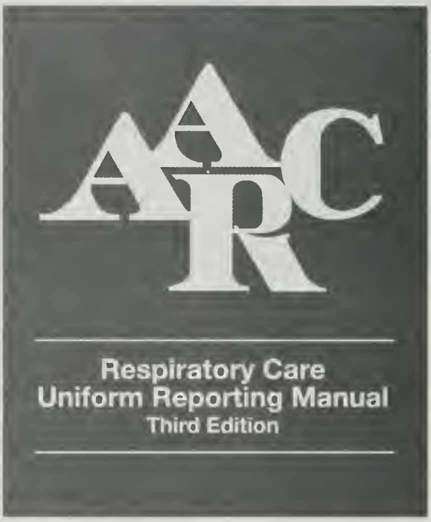

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On the Air Route*

Although this chapter, written only 30 years ago, may not qualify as history, it is a sort of medical landmark—a snapshot of one approach to improving the health of school children in the 1960s, and much (but not all) of the information could be offered today.

Crystal L Dunlevy EdD RRT

On Mouth Breathing

Since the nose is especially designed to act as an air conditioner, children should be encouraged to breathe through it. Those who are consistent mouth breathers should be referred to the nurse or the physician serving the school. The habit of mouth breathing almost always indicates that some sort of obstacle is interfering with nasal breathing. Mouth breathing has many disadvantages. An open mouth with droopy lower jaw gives the face a dull, vacuous expression, and many a bright child looks stupid if he is obliged to breathe through his mouth. The passage of air over the tongue has a drying effect, and the sense of taste may be blunted. Also interference with the aeration of the nose and sinuses may favor the development of infection.

On Pneumonia

Pneumonia is an extension of a respiratory infection into the air sacs (alveoli) of the lungs. It is in these tiny pouch-like blind endings of the smallest branches of the bronchial tree that the exchange of oxygen and carbon dioxide between the air and blood takes place. What happens is that the causative agents, or germs, get into places that cannot be kept clean by the moving mucous blanket of the respiratory passages. Pneumonia is invited and encouraged by anything that interferes with the normal escalator-like operation of this blanket, which, as we have seen, keeps virulent visiting pathogens from accumulating and mobilizing for invasion. That is why the development of pneumonia is so often associated with chilling of the body following exposure to cold and wet, with exhaustion from any cause, or, more especially, with a forerunning attack by the virus of the common cold or influenza virus.

On the Dangers of Cigarette Smoking

Shortly after the (Surgeon General's Advisory) Committee's report was published, two Harvard School of Public Health investigators announced that one natural contaminant of tobacco may prove to be the link between cigarette smoking and lung cancer. This contaminant is the radioactive element known as polonium 210. It occurs naturally in all green plants. Its danger to smokers lies in the fact that it vaporizes at the burning temperature of the cigarette and is carried into the lungs by attaching itself to smoke particles. For a man smoking two packs of cigarettes a day, the radiation dose to the bronchial linings from polonium 210 inhaled in cigarette smoke is at least seven times that of the normal radiation dose from background sources. It has long been known that radiation can produce cancer in man. Radiation from inhaled cigarette smoke may, therefore, act as an important initiator of bronchial cancer in smokers. Schools with comprehensive health education programs have for many years included whatever information was available on the harmful effects of smoking. Now that the cup of scientific and statistical evidence is full to overflowing, the opportunities for developing realistic educational programs that will appeal to the intelligence of thoughtful junior and senior high school students have been substantially increased.

On Protecting School Children from Airborne Infections

Correct Use of Handkerchiefs. The proper technique of coughing and sneezing is a form of good manners as well as a means of avoiding the broadcasting of infection. Children should be trained in this technique until it becomes habitual. The first requirement is the possession of a handkerchief. In blowing the nose, children should learn to blow gently, leaving both nostrils open so as to avoid the risk of driving the infection into the sinuses or middle ear. In coughing, the handkerchief should be held so that it completely covers both mouth and nose. In sneezing it is best to sneeze naturally through the mouth, with the handkerchief held as in coughing, rather than politely through the nose. Also, children should learn not to pull out used handkerchiefs with a flourish or to shake them. Experiments have shown that the shaking of dry used handkerchiefs releases thousands of germs into the surrounding air.

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* From Health Observation of School Children, 3rd ed. McGraw-Hill: New York, 1965 by George M Wheatley MD MPH and Grace T Hallock. Dr Wheatley was Third Vice President and Medical Director, Metropolitan Life Insurance Co, Division of Health and Welfare. Ms Hallock coauthored the series entitled, Health for Better Living, Health for Life, and Health Heroes.

This excerpt was made available to RESPIRATORY CARE by Dr Dunlevy who is Associate Professor and Director of Clinical Education, Respiratory Therapy Division, School of Allied Medical Professions, The Ohio State University, Columbus, Ohio.

Proper Seating. Children should be seated as far apart as possible. During epidemics, advantage should be taken of empty seats to increase the spacing.

Good Ventilation. Whatever the heating and ventilating arrangements of the school are, provision should be made to keep the air of occupied classrooms constantly in motion. Moving air helps to break up concentrations of airborne germs.

Hand-Washing Facilities. Although hand washing may not materially affect the spread of airborne infection, it is a good hygienic habit for children to form. The facilities required to make hand washing effective are warm water (preferably running water from a tap), soap, and individual cloth or paper towels.

School Cleaning. Airborne germs in droplet nuclei or on dust particles eventually settle on the floor and on furniture. They are given a second chance to find victims if they are stirred into the atmosphere during cleaning. The floor and furniture finishes and the methods of cleaning in modern schools reduce the raising of dust to a minimum. In schools without these improvements, the use of damp sweeping and damp dusting is recommended as a means of reducing the contamination of air by germs.

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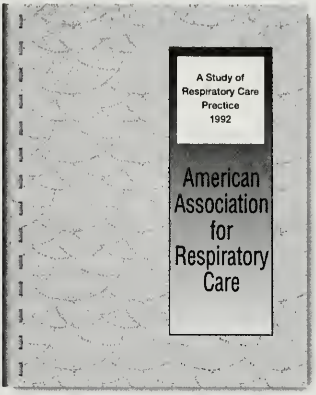
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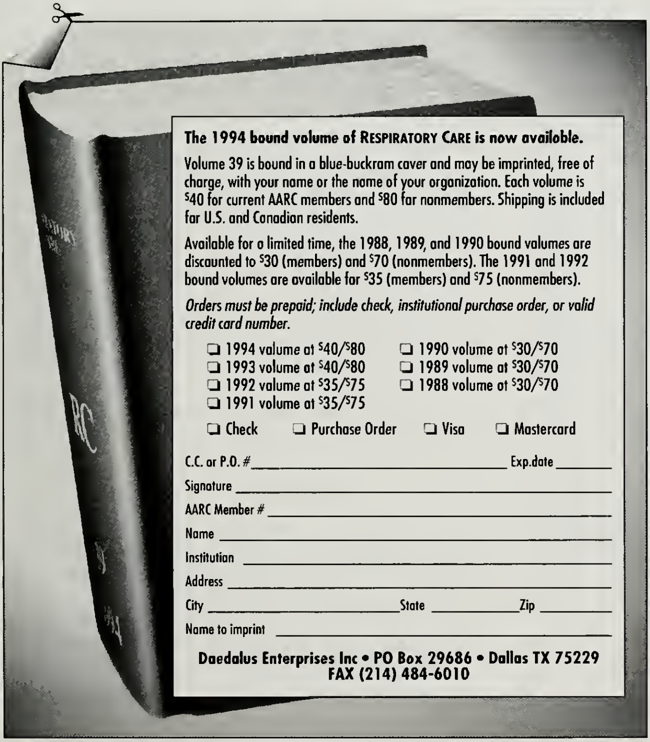

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6. Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

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7. Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

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8. Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Paper accepted but not yet published:

9. Hess D. New therapies for asthma. Respir Care (year, in press).

Personal author book: (For any book, specific pages should be cited whenever possible.)

10. DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura, 1990:76-85.

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11. American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group, 1977.

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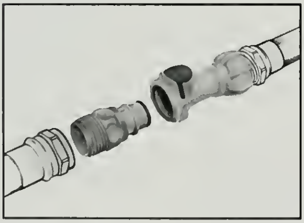

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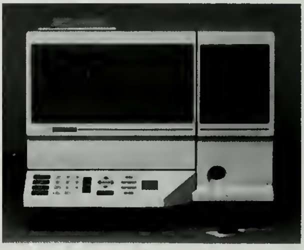
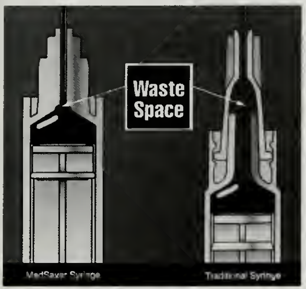
ONE-WAY-VALVE MOUTHPIECE. Safety mouthpieces that offer protection from cross-contamination during multipatient screening with ASSESS® peak flow meters are available from HealthScan Products. The cardboard mouthpieces have a patented one-way valve that prevents patients from accidentally breathing air through ASSESS during peak expiratory flow rate testing. For details about the peak flow meter or the safety mouthpiece, call HealthScan Products Inc at (800) 962-1266. Don't forget to mention RESPIRATORY CARE.

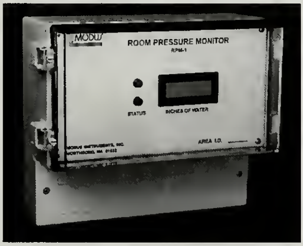
EDUCATIONAL VIDEO. Glaxo Inc's Medical and Professional Education division presents a new 16-minute video, *Tuberculosis—Return of an Ancient Killer*. Suitable for all health-care professionals, the video explores the reappearance of tuberculosis in the US, multidrug-resistant strains of tuberculosis and poor patient compliance with appropriate therapy. According to the producers, worldwide, tuberculosis causes more deaths than any other pathogen. To obtain the video, ask a Glaxo sales representative or write to Glaxo Inc, Dept RC, 5 Moore Drive, Research Triangle Park NC 27709. Please mention RESPIRATORY CARE when calling (800) 824-2896.



MULTITEST ANALYZER. Nova Biomedical releases the Stat Profile Ultra®. The unit consolidates the test menus of 5 separate laboratory analyzers to measure up to 11 of the most frequently ordered stat tests. The analyzer provides results for P_{O_2}, P_{CO_2}, pH, $SO_2\%$, sodium, potassium, glucose, hematocrit, ionized calcium, ionized magnesium, and lactate. Nova claims the Stat Profile Ultra reduces turnaround times, improves patient outcomes, reduces costs, increases patient survival, and reduces transfusions. In addition, the unit features automatic calibration and sampling, a test menu, on-board quality control, patient data storage, and password protection. The analyzer is available with a Windows®-based, Patient Data Management option. For more information, write to Nova Biomedical, Dept RC, 200 Prospect Street, Waltham MA 02254. Mention RESPIRATORY CARE when calling (617)894-0800.



Syringe. Becton Dickinson and Company introduces a new low-waste syringe. The newly designed MedSaver Syringe has a permanently attached needle that eliminates the syringe tip and needle hub. According to the manufacturer, this special design provides cost savings by increasing the number of doses in multidose vials of vaccines and medications used in intramuscular injections. The syringe comes in 6 combinations of volume, gauge, and needle length For more information, write to Becton Dickinson and Company, Dept RC, 1 Becton Drive, Franklin Lakes NJ 07417-1884. When calling (201) 847-4000, please mention Respiratory Care.



Room Pressure Monitor. A room pressure monitor, Model RPM-1, is Modus Instruments new release. The device uses an advanced sensor technology to monitor room-to-room differential pressures and is particularly suited for clean room, hospital, biomedical and research applications where negative or positive room pressures are controlled. According to Modus, the monitor operates by switching to a red indicator light when a preset pressure switch is triggered. An LCD display indicates the value of the room pressure in English or metric units. The monitor can be expanded to include an alarm or analog output. Both may be used to record data. Information is available by writing to Modus Instruments Inc, Dept RC, 10 Bearfoot Road, Northborough MA 01532, or by calling (508) 393-8991. Please mention Respiratory Care.

Nasal CPAP System. DeVilbiss Health Care Inc, a division of Sunrise Medical, releases a new Nasal CPAP System, Horizon.™ According to DeVilbiss, the unit is compatible with its Seal-Ring™ and CPAP Mask kit. For use in both home and clinical settings, the Horizon can provide remote polysomnographic outputs for snoring events, mouth breathing, and mask leaks. In addition, the unit is equipped with a 1-year utilization meter that provides a daily usage history. Other features are a breathing activation system for easy starts, a pressure-delay system for gradual transitions for a 10-, 20-, or 30-minute period, and a microprocessor blower control system for adjusting to pressure changes and maintaining prescribed pressure levels. For details, write to DeVilbiss Health Care Inc, Dept RC, PO Box 635, Somerset PA 15501-0635, or call (800) DeV-1988 in the U.S. or (800) 263-3390 in Canada. Please mention Respiratory Care when you call.

Management System. Burdick Inc introduces the PYRAMIS ECG Management System, a powerful system with cost-effective, time-saving features for hospital ECG tracking, editing, and storage. According to the product manufacturer, the system was developed around client-server technology for maximum power, speed, and flexibility. The management system features a standard communication protocol, bidirectional communication, a high speed modem to facilitate ECG transmission, and bar coding capabilities for patient information. In addition, the system saves time with demographic editing capabilities, batch processing, and remote workstations as well as the ability to interface with hospital information systems. The system provides storage for over 1 million ECGs and can easily be upgraded. For details contact Burdick Inc, Dept RC, Rolling Meadows IL 60008 or call (800) 955-5177. Remember to mention Respiratory Care when calling.

PEP Therapy System. According to Diemolding Healthcare Division, their new TheraPEP is the first system designed specifically to promote secretion clearance through positive expiratory pressure therapy. This therapy helps mobilize secretions in COPD, CF, and post-operative patients who are unable to tolerate conventional chest physical therapy. The system features a pressure indicator for immediate visual feedback, six orifice options for prescribing the resistance level, and a design that may be used with a mask or mouthpiece. For more information, write to Diemolding Healthcare Division, Dept RC, 125 Rasbach Street, Canastota NY 13032 or call (800) 847-8000. Don't forget to mention Respiratory Care.

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

1995 Publication Awards

$1,000
Radiometer Awards for Best Feature Articles
from Test Your Radiologic Skill,
Blood Gas Corner, Kittredge's Corner,
and PFT Corner
accepted for publication from
November 1994 through October 1995
Sponsored by Radiometer America
(Divided equally among three winners)

$1,000
Best Papers by 1994 OPEN FORUM Participants
Who Have Never Published as First Author
Authors must present the abstract at the Annual Meeting
and submit a paper based on the abstract to the
Editorial Office by November 1, 1995
Sponsored by Allen & Hanburys
(Two winners - $500 each)

$2,000
Best Papers on OPEN FORUM Presentation
Papers accepted for publication from
November 1994 through October 1995
based on any Open Forum presentation
Sponsored by Allen & Hanburys
(Two winners - $1,000 each)

$2,000
Best Paper Published in RESPIRATORY CARE
Original Study, Evaluation, or Case Report
are the categories for consideration for papers
accepted for publication
December 1994 through October 1995
Sponsored by Allen & Hanburys

$2,000
Dr Allen DeVilbiss Technology Paper Award
Best paper published from
November 1994 through October 1995
that addresses new technology or a new application of
current technology in respiratory care
(Plus travel expenses to the
AARC Annual Convention & Exhibition)

Respiratory Care Week

October 1-7, 1995

Ideas and products for Respiratory Care Week
are available in the
1995 RC Week Catalog,
mailed with the June issue of *AARC Times*.
Call the RC Week hotline at
(214) 243-1478.

FACE TO FACE WITH CHANGE

AARC 41st Annual Convention
& Exhibition
Orlando, Florida
December 2-5, 1995

Look for this year's program in the
September issue of the *AARC Times*.

Advance programs will be mailed
September 13, 1995.
The registration deadline is
November 11, 1995.

The National Board for Respiratory Care

8310 Niemann Road
Lenexa KS 66214

For information about
1995 or 1996
Examination & Fee Schedules
call
(913) 599-4200
or FAX
(913) 541-0156

MEDWATCH
HE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting
by health professionals of adverse
events and product problems

Page ____ of ____

Form Approved. OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only (RESP CARE)

Triage unit
sequence #

A. Patient information

Patient identifier In confidence	2. Age at time of event: ____ or Date of birth:	3. Sex ☐ female ☐ male	4 Weight ____ lbs or ____ kgs

3. Adverse event or product problem

☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

Outcomes attributed to adverse event
(check all that apply)

☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)

Describe event or problem

Relevant tests/laboratory data, including dates

Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 ____
#2

2. Dose, frequency & route used
#1 ____
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 ____
#2

4. Diagnosis for use (indication)
#1 ____
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 ____
#2

7. Exp. date (if known)
#1 ____
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ____

5. Expiration date (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4 Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

DA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

• 1-800-FDA-0178	to FAX report
• 1-800-FDA-7737	to report by modem
• 1-800-FDA-1088	for more information or to report quality problems
• 1-800-822-7967	for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send your comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building.
Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
ATTN: PRA

and to:
Office of Management and Budget
Paperwork Reduction Project
(0910-0230)
Washington, DC 20503

Please do NOT return this form to either of these addresses.

FDA Form 3500-back

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Public Health Service
Food and Drug Administration
Rockville, MD 20857

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MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

1996 Call for Abstracts

RESPIRATORY CARE • OPEN FORUM

The American Association for Respiratory Care and its science journal, RESPIRATORY CARE, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present posters at the OPEN FORUM during the AARC Annual Meeting in San Diego, California, November 3-6 1996. Accepted abstracts will be published in the October 1996 issue of RESPIRATORY CARE. Membership in the AARC is not required for participation.

SPECIFICATIONS—READ CAREFULLY!

An abstract may report **(1) an original study, (2) the evaluation of a method or device, or (3) a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, or health-care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract will be the only evidence by which the reviewers can decide whether the author should be invited to present a poster at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write such general statements as "Results will be presented" or "Significance will be discussed."

Essential Content Elements

Original study. Abstract *must* include (1) Background: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results.

Method/device evaluation. Abstract *must* include (1) Background: identification of the method or device and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience or a lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate.

Case report. Abstract *must* report a case that is uncommon or of exceptional educational value and must include (1) Introduction: Relevant basic information important to understanding the case. (2) Case Summary: Patient data and response, details of interventions. (3) Discussion: Content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

Abstract Format and Typing Instructions

Accepted abstracts will be photographed. The first line of the abstract should be the title in all capital letters. Title should explain content. Follow title with names of all authors (including credentials), institution(s), and location. Underline presenter's name. Type or electronically print the abstract *single spaced in the space provided on the abstract blank.* Insert only one letter space between sentences. Text submission on diskette is encouraged but must be accompanied by a hard copy. Identifiers will be masked (blinded) for review. Make the abstract all one paragraph. Data may be submitted in table form, *and simple figures may be included provided they fit within the space allotted.* No figures, illustrations, or tables are to be attached to the abstract form. Provide all author information requested at the bottom of abstract form. A clear photocopy of the abstract form may be used. Standard abbreviations may be employed without explanation. A new or infrequently used abbreviation should be preceded by the spelled-out term the first time it is used. Any recurring phrase or expression may be abbreviated, if it is first explained. Check the abstract for (1) errors in spelling, grammar, facts, and figures; (2) clarity of language; and (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed. Questions about abstract preparation may be telephoned to the editorial staff of RESPIRATORY CARE at (214) 243-2272.

Deadline Allowing Revision

Authors may choose to submit abstracts early. Abstracts postmarked by February 11, 1996 will be reviewed and the authors notified by letter only to be mailed by March 22, 1996. Rejected abstracts will be accompanied by a written critique that should, in many cases, enable authors to revise their abstracts and resubmit them by the final deadline (April 28, 1996).

Final Deadline

The mandatory Final Deadline is April 28 (postmark). Authors will be notified of acceptance or rejection *by letter only.* These letters will be mailed by July 15, 1996.

Mailing Instructions

Mail (Do not fax!) 2 clear copies of the completed abstract form, diskette (if possible), and a stamped, self-addressed postcard (for notice of receipt) to:

RESPIRATORY CARE OPEN FORUM
11030 Ables Lane
Dallas TX 75229-4593

1996 RESPIRATORY CARE OPEN FORUM

Abstract Form

18.8 cm or 7.4"

13.9 cm or 5.5"

1. Title must be in all upper case (capital) letters, authors' full names and text in upper and lower case.
2. Follow title with all authors' names including credentials (underline presenter's name), institution, and location.
3. Do not justify (ie, leave a 'ragged' right margin).
4. **Do not use type size less than 10 points.**
5. All text, tables, and figures must fit into the rectangle shown.
6. Submit 2 clean copies. This form may be photocopied if multiple abstracts are to be submitted.

Mail original &
1 photocopy
(along with postage-
paid postcard) to

**RESPIRATORY CARE
OPEN FORUM
11030 Ables Lane
Dallas TX 75229-4593**

*Early deadline is
February 11, 1996
(postmark)*

*Final deadline is
April 28, 1996
(postmark)*

Presenter

Name & Credentials

Mailing Address

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Name & Credentials

Mailing Address

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Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Calendar of Events

AARC & AFFILIATES

September 19 AARC Videoconference. The AARC, in conjunction with VHA Satellite Network, presents the 6th installment of the 7-part "Professor's Rounds in Respiratory Care" videoconference series. This conference, "Organizing a Respiratory Care Department Without Walls," focuses on how to establish respiratory services in the post-acute-care setting. Each videoconference in the series airs from 12:30-2 p.m. Eastern Time; viewers of the live presentation receive 1 hour of CRCE credit. For information, call VHA Satellite Network at (214) 830-0061.

September 21–22 in Napa, California. Chapter 10 of the CSRC, the American Lung Association of the Redwood Empire and the Respiratory Therapy Program at Napa Valley College present the 13th Annual Napa Valley Conference. Topics include therapist-driven protocols, primary care concerns in HIV, sleep-related breathing disorders, pediatric trauma triage, and ethics in ventilator termination. Contact Kate Benscoter at (707) 253-3145.

September 21–22 in Pittsburgh, Pennsylvania. The Southwest District of the PSRC announces the 22nd Annual Physiology and Medicine Meeting at the Sheraton Hotel, Station Square. Specialty tracts include management, nursing, and a new continuum-of-care tract. Contact St Francis Medical Center's Continuing Medical Education at (412) 622-4100.

September 22–23 in Chicago, Illinois. The AARC announces the Regional Seminar — "Creating Tomorrow's Respiratory Care Department...Today!" — at the Chicago O'Hare Marriott. The seminar for managers and staff describes strategies to make changes, adapt to them, and survive in tomorrow's (and today's) health-care system. Specific presentations include "RCP 2001: Future-Casting the Needs of the Health Care System of the Future," "The Clinical Side: How Patient Care Services Are Changing in Respiratory Care Departments," and "Putting It All Together: Making Money, Saving Money, Expanding Services." The seminar is approved for up to 10 hours of CRCE credit. Call the AARC Executive Office at (214) 243-2272 or fax (214) 484-2720 for program information.

September 26–27 in Honolulu, Hawaii. The HSRC and the American Lung Association of Hawaii host the 22nd Annual Respiratory Care Conference at the Hilton Hawaiian Village Hotel. Topics include treatment of airway obstruction by therapist-driven protocol, clinical trials in liquid ventilation, an update on high-frequency ventilation, newer forms of mechanical ventilation by protocol, and metabolic monitoring. Contact Wendell Inouye RRT, at Kapiolani Medical Center for Women and Children, (808) 973-8689, fax (808) 973-4730.

October 5–6 in Albany, New York. The Northeastern Chapter of the NYSSRC hosts its Annual Teaching Day at the Desmond Inn. Featured topics include lung reduction surgery, management of the difficult airway, and current concepts in pediatric asthma therapy. Other events include Sputum Bowl competitions and an open forum panel of area pulmonologists. Contact Dawn Bentley or Bill Wenzel, Respiratory Care Department, St Peter's Hospital, 315 S Manning Blvd, Albany NY 12208, (518) 454-1062.

October 11–13 in Columbus, Ohio. The OSRC announces its 19th Annual Meeting at the Holiday Inn Conference Center at Worthington. Featured discussions include clinical care of the patient and current topics affecting respiratory care. Breakout sessions are available in management, student education, and blood gas laboratory management. CRCE credit has been requested. Contact Dan Wine, Program Planning Chairman, Respiratory Care Department, Grady Memorial Hospital, 561 W Central Ave, Delaware OH 43015, (614) 368-5315.

October 13 in Colorado Springs, Colorado. The Southern Chapter of the CSRC presents the 2nd Annual Southern Colorado Pulmonary Medicine Symposium at the Holiday Inn, Garden of the Gods. Topics include neonatal ventilation, partial liquid ventilation of the adult, current trends in sleep disorder management, and reactive airways disorders in respiratory therapists. Registration is $15 and includes lunch; participants can earn up to 5 hours of CRCE credit. Contact Barry Beard at (719) 776-5211.

October 13 in Pikeville, Tennessee. The TSRC presents its 2nd Annual Fall Fest at Fall Creek Falls State Park. Topics include benchmarking and developing critical pathways. Contact Colleen Schabacker at (615) 384-1731.

October 13–14 in Boise, Idaho. The ISRC hosts its annual educational fall meeting, "Surviving Change," at the Red Lion, Riverside, in conjunction with the 2nd Annual John Butler Lung Conference. The fee for AARC members is $30; CRCE credit has been requested. Contact Leslie Ann Mulder at (208) 336-3391.

October 20 in Uniondale, New York. The Southeastern Chapter of the New York State Society for Respiratory Care hosts its 27th Annual Symposium at the Marriott Hotel. The symposium, "The Wheel of Change—Are We Prepared?" features a managers' breakfast, 50 exhibitor booths, and the annual awards luncheon. Contact Ralph Cavallo at (212) 523-3101 or Michael Karol at (718) 470-7680.

OTHER MEETINGS

September 27 in Palm Beach Gardens, Florida. The American Lung Association (ALA) of Southeast Florida announces its Asthma Management Symposium from 7:45 AM to 3:45 PM at the Palm Beach Gardens Marriott. The course covers recent developments in the diagnosis and management of asthma, including compliance, barriers to compliance, the role of the family, and medications and proper administration. The course is approved for 6 Category I hours of CRCE credit. Contact the ALA of Southeast Florida at (407) 659-7644.

October 5–6 in Asheville, North Carolina. The Mountain Area Health Education Center presents the 7th Annual Mountain Air Conference at the center. The agenda includes pediatric sessions as well as sessions on pulmonary monitoring in ventilator patients, managing stress, and heavy sedation vs paralysis in ICU patients. Dr Forrest Bird presents the keynote address, "Cardiopulmonary Management: The State of the Art." Call (704) 257-4473 for more information.

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DHD Diemolding Healthcare Division 906
Circle Reader Service No. 111 — Call (800) 847-8000
Dräger 913
Circle Reader Service No. 101 — Call (703) 817-0100
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Circle Reader Service No. 118 — Call (800) 962-1266
HealthScan Products Inc 922-923
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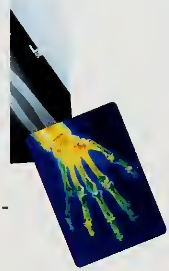

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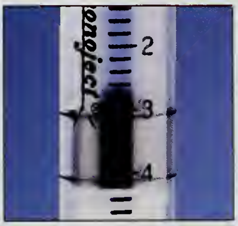

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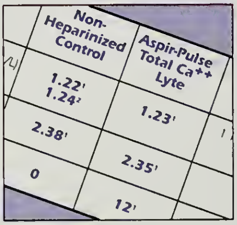

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